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Thesis

# PHYSIOLOGY OF THE DIGESTIVE GLANDS IN MAMMALIA

Submitted by

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(Ph.B., Providence College,1928)

In partial fulfilment of requirements for

the degree of Master of Arts

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# PHYSIOLOGY OF THE DIGESTIVE GLANDS IN MAMMALIA

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# - INTRODUCTION -

In view of the chief duty which the digestive tract has to perform in the living organism, Pavlov has adequately compared it to a chemical factory, where the raw materials - the food-stuffs - are submitted to an essentially chemical process. They are so brought into a condition in which they are capable of being absorbed into the body fluids and made use of for the maintenance of life.

"This factory," says Pavlov, "consists of a series of compartments where the food, according to its properties, is either retained for a time or at once sent on to the next. The factory and, indeed, each single compartment is provided with suitable reagents. These are either prepared in neighboring little workshops, buried in the walls of the structure itself, or else in distant and separate organs which are connected, as in other large chemical factories, with the main laboratory by a system of transmitting tubes. These latter are the so-called secreting glands with their excretory ducts. Each of the work-shops furnish a specific fluid, its own particular reagent, endowed with definite chemical properties which only act on certain portions of the foods, this latter being ordinarily formed of a complex mixture of different ingredients. These properties are chiefly determined by the presence of special substances in the reagents, the so-called ferments. The separate fluids, the digestive juices as they are usually termed, attack at one time only a single ingredient of the food, at another time, several. Thus, they combine the properties of many individual reagents, each of which acts in its own special way."

Physiology has been able to gain a comprehensive knowledge of the digestive apparatus by obtaining either the fluids in question, or the pure ferments from the organism, and studying, in the test-tube, their effects upon the constituents of the foods as well as their behavior toward each other.

Many questions, however, that touch upon the vital facts have still remained undecided. The subject of dietetics represents one of the most intricate sections of therapeutics. It is not enough for the physiologist to have a knowledge of the separate elements concerned in the process of digestion, i.e. the working of individual agencies, but, in order to grasp his subject fully, he must also include within the sphere of his observations the actual progress of digestion as a whole. Many investigators would, doubtless, have accomplished the solution of the problem had it been of easier description.

# PHYSIOLOGY OF THE DIGESTIVE GLANDS IN MAMMALIA.

## 1. THE SALIVARY GLANDS

In Mammalia there are a number of glands the secretions of which play a part in the digestion of food. A series of complex reactions take place from the moment the food enters the mouth cavity until it is finally absorbed and assimilated into the blood stream from the intestinal tract. The first of the secretions which the food comes into contact with is the saliva, a mixed secretion from the large salivary glands that open into the mouth cavity.

The salivary glands are three in number on each side of the head - the parotid, the submaxillary, and the sublingual. The parotid occupies the space in front of the ear, resting with its flattened inner surface upon the soft parts covering the ramus of the mandible. It communicates with the mouth by a duct (Stenson's Duct) opening upon the inner surface of the cheek opposite the second molar tooth of the upper jaw. The submaxillary lies below the lower jaw with its duct (Wharton's Duct) opening into the mouth cavity at the side of the frenum of the tongue. The sublingual lies in the floor of the mouth at the side of the frenum with a series of ducts (8-20) known as the ducts of Rivinus, opening into the mouth cavity.

The salivary glands receive their nervous stimuli from two general sources: viz. the cerebral fibers or the bulbar autonomics and the sympathetic autonomics. The parotid gland receives its bulbar autonomics from the glosso-pharyngeal or the ninth cranial nerve; they pass to a branch known as the tympanic branch, thence to a small superficial nerve through which they reach the otic ganglion.

From this ganglion they pass by way of the branch of the inferior maxillary division of the fifth cranial nerve to the parotid gland. The bulbar autonomic impulses for the submaxillary and sublingual glands arise in the brain in the facial nerve and leave by way of the chorda tympani branch. This nerve, after leaving the tympanic cavity, joins the lingual nerve and after running with this nerve for a short while, the secretory nerve fibers for the submaxillary and sublingual glands branch off and pass to the glands.

## Histological Structure of the Salivary Glands.

According to secretion the salivary glands are divided into: mucous, serous, and mixed. The mucous glands are distinguished by their large secretory units. These are called "acini", "alveoli" or "tubules", and produce a thick, viscid secretion. These glands are found in the mouth, pharynx and esophagus. The sublingual is almost a pure mucous gland. Serous glands are those in which the acini stain darkly owing to the presence of the secretory granules in the cytoplasm. The acini are usually smaller than those of the mucous glands. The mixed glands are those which stain both lightly and darkly and secrete a mixed fluid as do the submaxillary and sublingual.

All of these glands have the same general structure. Each is surrounded by a capsule of white fibrous tissue that separates it from the surrounding organs or tissues. The capsule sends out prolongations that divide the gland into lobes and lobules. The lobules consist of the functionating units that are composed of a single layer of glandular epithelial cells, called "parenchyma", supported by a basement membrane. External to the basement membrane is the interstitial or interlobular connective tissue, com-

posed of reticulum, (a special arrangement of the areolar form of connective tissue) and in which the blood vessels, nerves and lymphatics are found. The secretory units lead into minute intermediate or intercalated tubules that unite to form interlobular ducts which pass into the interlobular connective tissue. The interlobular ducts, by union, form the lobars and then the single excretory duct. The intermediate tubules are lined by a simple squamous or low columnar cells supported by a membrane and interstitial tissue; the interlobular branches contain simple columnars, the interlobulars and interlobars are lined by pseudo-stratified columnars, and the excretory duct usually by stratified columnars.

The blood-vessels follow the division of the ducts and form plexuses of capillaries around the secretory units and in close proximity to the epithelium. The nerves pass down in the same manner and after penetrating the basement membrane end around the cells.

The parotid gland is a compound aveolar gland and is divided into lobes and lobules as described. It is the largest oral salivary gland. In each lobule are found the secretory units or acini which are serous in character, the intercalated and interlobular ducts. Each acinus consists of a number of small darkly stained cells of a pyramidal shape, arranged in a single layer upon the thin basement membrane. In the center of this group of cells is a "lumen" the size of which depends upon the stage of activity of the gland. The acini are comparatively small. The basement membrane contains small basket cells at the bases of the epithelial cells, and the processes of these basket cells pass between the functionating epithelium. These are assumed to be the young secreting cells replacing the older ones that cease to function.

The cytoplasm of the secreting cells is nearly clear and finely granular in the early resting stage; during the latter part the granules increase in number and a small amount of clear cytoplasm and the nucleus occupy the basal portion of the cell. The cell becomes so swollen as to block the lumen and, as these zymogen granules are discharged during the active stage, the cells become smaller and the granules nearly all disappear; the cytoplasm increases in amount and spreads through the cell. In the cytoplasm and between the cells there is a set of secretory capillaries or "canaliculi". The acini pass the secretion to the intercalated tubules that are lined with squamous cells and these join the interlobular ducts that are lined with low columnar elements. These in turn empty into the interlobular ducts that lie in the interlobular connective tissue. These are larger in caliber and are lined with columnar cells and possess three coats. A great deal of adipose tissue is found in the interlobular tissue of the parotid gland.

The submaxillary gland is a tubuloalveolar gland in structure and a mixed gland in secretion. The mucous tubules may be collected in individual lobules or they may be mixed with the serous acini. The serous acini are supposed to be five times as numerous as the mucous tubules in man. The mucous tubules, however, are the larger of the two. The cells are of the columnar variety, are quite large and stain but lightly. The cytoplasm in the fresh condition is clear and refractile. In properly fixed tissue the cytoplasm contains a coarse reticulum that is basophilic in reaction and is situated mainly in the lumen portion of the cell. The cytoreticulum contains coarse granules that respond to special mucin stains. These granules increase in number during the resting

stage and the cells become larger and assume a swollen appearance. When the secretion is to be discharged, water from the lymph between the cells passes into the cells, the granules swell and are dissolved and the secretion is discharged. The cell then becomes smaller. In a full cell, the nucleus and a little finely granular cytoplasm are forced against the base of the cell. When the secretion is discharged, the nucleus moves away from the base and the cytoplasm spreads through the distal extremity of the cell. In most of the mucous and mixed glands in these tubules, other cells are found between the mucous cells and the basement membrane. These are darkly staining cells arranged in the form of crescents and constitute the "crescents of Gianunzi" or the "demilunes of Heidenhain". These groups are chiefly located at the blind extremity of the mucous tubules and, even though at times they may reach to the lumen, they are usually separated from them by the mucous cells. The intracellular and intercellular capillaries are numerous; the secretion is discharged from the former into the latter and through these reaches the lumen of the tubule. Hence, they resemble true serous cells, and Krausé has shown that these cells will discharge sodium indigo sulphate granules as do the serous cells. The interlobular ducts are unusually large and distinct in some animals and often represent a distinguishing feature of this gland.

The sublingual is a collection of glands and not an individual organ in the floor of the oral cavity. It is the smallest of the salivary glands, each mass weighing only three to four grams. In structure it is compound tubular and nearest to the pure mucous glands as it does not contain any serous acini; the serous portion

is represented by the crescents of Gianuzi. Oftentimes, sections of serous acini are apparently seen, but these are said to be cross-sections of the tubules near the blind end in which the crescents abound. There are usually several ducts, called the sublingual ducts or the "ducts of Rivinus". Should only one be present, it is called the "duct of Bartholin".

## Histological Changes During Activity.

The cells of both albuminous and mucous glands undergo distinct histological changes as a result of their prolonged activity. In the resting gland, the cells are comparatively filled with granules that stain readily and are imbedded in a clear ground substance that does not stain. The nucleus is small and irregular in outline. After stimulation of the chorda tympani nerve, the cells show but little alteration; however, stimulation of the sympathetic produces a marked change, the cells become smaller, the nuclei more rounded, and the granules are more closely packed together.

Langley[1] was the first to obtain specific data from the study of fresh glands, and gives the results of the experiment as follows: "When the animal is in a fasting condition, the cells have a granular appearance throughout their substance, the outlines of the cells being faintly marked, as shown in Fig. 1. When the gland is made to secrete by giving the animal food, by injecting pilocarpine, or by stimulating the sympathetic nerves, the granules begin to disappear from

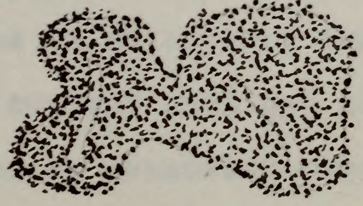

Fig. 1.

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[1] "Journal of Physiology," 2,260,1879.

the outer border of the cells, so that each cell shows an outer, clear border and an inner granular one, as is shown in Fig. 2. If the stimulation is continued, the granules become fewer in number and are collected near the lumen and margins of the cells, the clear zone increases in extent, and the cells become smaller, as is shown in Fig. 3." The granular material is evidently used in some way to make the organic material of the secretion. Since the ptyalin is a conspicuous organic constituent of the secretion, it is assumed that the granules in the resting stage contain the ptyalin, or the preliminary material from which the ptyalin is constructed, during the act of secretion. Based upon this assumption, the granules are spoken of as "zymogen granules."

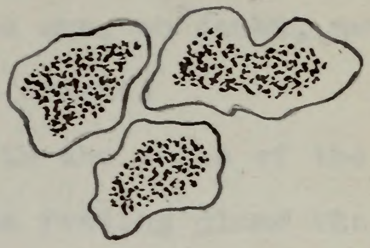

Fig. 2.

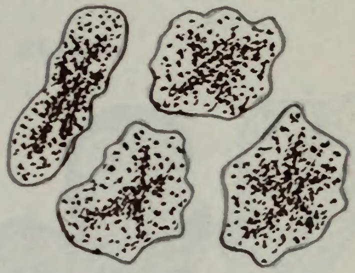

Fig. 3.

During the process of secretion, there are two distinct processes which seem to be going on within the cell; first of all, the zymogen granules undergo a change such that they are forced or dissolved out of the cell; secondly, a constructive metabolism is set up leading to the formation of new protoplasmic material from the substance contained in the blood and lymph. The new material thus formed is the clear non-granular substance which appears first toward the basal side of the cell. We may suppose that the clear substance during the resting period undergoes metabolic change, whether the changes are of a metabolic or a katabolic character cannot be asserted safely, leading to the formation of new granules

and the cells are again ready to form a secretion of normal composition. In these experiments the glands were stimulated beyond normal limits. Under ordinary conditions, the cells are, no doubt, never depleted of their granular material to a great extent.

Changes equally marked may be observed in the cells of the mucous glands after prolonged activity. In the resting gland the cells are large and clear with flattened nuclei situated well towards the base of the cell. A mucous glad, the submaxillary of the dog, is shown in Fig. 4. as it appears in the resting stage.

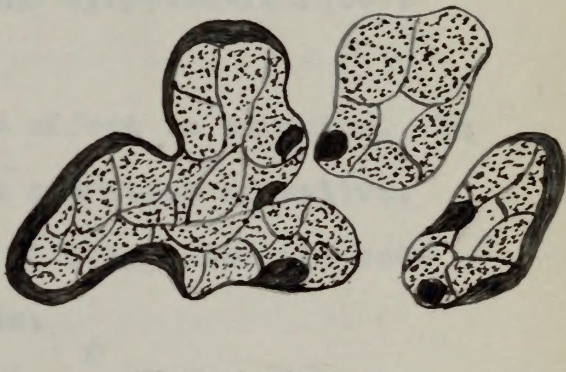

Fig. 4.

When the gland is made to secrete, the nuclei become more spherical and are situated more toward the middle of the cell, which themselves become distinctly smaller. The changes become more marked after prolonged secretion and some of the mucous cells may break down completely. The submaxillary gland of the dog is shown in Fig. 5. as it appears after prolonged stimulation of the chorda tympani. According to some observers, the mucous cells do not disintegrate but form new material during the period of rest. Langley has shown that in the fresh mucous cells of the submaxillary gland, about 125 to 250 large granules may be found to a cell. These granules are comparable to those in the goblet cells and may be supposed to contain mucin or some material from which mucin is formed. The granules are particularly sensitive to reagents, the addition of water causing them to swell and disappear.

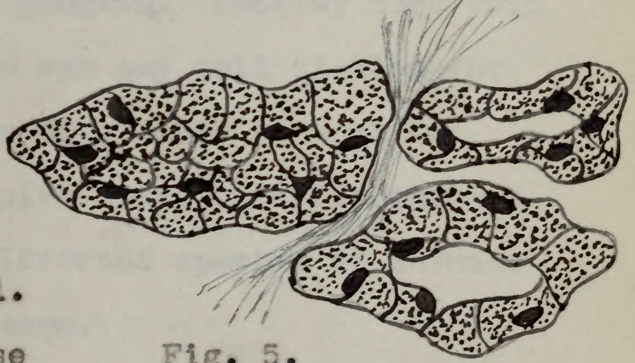

Fig. 5.

The action of certain drugs as atropine, pilocarpine and nicotine upon the salivary glands has a peculiar physiological interest. Small doses of atropine injected either into the blood or into the gland duct inhibit the action of the tympanic nerve upon the glands. This effect may be attributed to the fact that atropine paralyzes the endings of the cerebral fibers in the glands. It does not act directly upon the gland cells themselves since doses sufficient to throw out entirely the secreting action of the cerebral fibers being administered, the sympathetic fibers are still effective when stimulated.

Pilocarpine has exactly the opposite effect to atropine. In very small doses it produces a continuous secretion of saliva, which may be attributed to the fact that it stimulates the endings of the secretory fibers in the glands.

According to the experiments of Langley,[2] nicotine inhibits the action of the secretory nerves by paralyzing the connections between the preganglionic and the postganglionic fibers. The effect of the drug is exerted, apparently, on the synapse and does not confine itself to the sympathetic ganglia. Langley used this knowledge in discovering whether there was any cell station for given fibers in any place to which the drug could be applied.

Synapses of different nerves require doses of different concentrations, and the sensibility of different species of animals to the action of the drug is not the same.

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2. "Proceedings of the Royal Society," London, 46,423,1889.

## Composition of Secretion

The saliva as found in the mouth is a colorless, viscid liquid with a specific gravity of about 1.003 and a neutral or slightly acid reaction. It sometimes contains a number of flat cells from the epithelium of the mouth and the peculiar spherical cells known as salivary corpuscles.

The important constituents of the secretion are mucin, ptyalin, maltase, traces of protein and potassium sulphocyanide, and inorganic salts such as potassium and sodium chloride, potassium sulphate, sodium carbonate and calcium carbonate. The carbonates are abundant in the secretion and also carbon dioxide in solution.

The mucin in the saliva gives it its ropy, mucilaginous character. This substance belongs to the group of combined proteins and glyco-proteins consisting of a protein combined with a carbohydrate group. The most interesting constituent of the mixed saliva is the ptyalin or salivary diastase which belongs to a group of enzymes or unorganized ferments.

Upon examinstion of the separate secretions, we observe that the main difference lies in the fact that the parotid saliva contains no mucin but is rich in ptyalin, while the submaxillary and sublingual secretions are rich in mucin.

## Normal Mechanism of the Secretion.

The flow of saliva under normal conditions from the glands is due to a reflex stimulation of the secretory nerves. The sensory fibers concerned in this reflex must be chiefly fibers of the glossopharyngeal and lingual nerves supplying the mouth and tongue. Section of the chorda tympani prevents the reflex

in spite of the fact that the sympathetic fibers are still intact. Various authors have suggested that possibly the three salivary glands respond normally to different stimuli.

According to Pavlov, in his thesis "The Work of the Digestive Gland", in the dog the parotid and the submaxillary may react quite differently. Fistulas were made of the ducts of these glands and it was seen that the submaxillary responded readily to a number of stimuli, such as the sight of foods, chewing of meats, acids, etc. The parotid, however, reacted only when dry food, dry powdered meat, or bread was placed in the mouth. Dryness, in the case of the parotid, seemed to have been the efficient stimulus.

Great stress was laid by Pavlov[3] upon the adaptability of the secretion of saliva to the character of the material chewed. Dry, solid food stimulates a large flow of saliva as it is necessary to chew it properly and form it into a bolus for swallowing. Foods which contain a great deal of water, on the contrary, stimulate but little the flow of saliva. Such adaptation, according to Pavlov, must be regarded from the psychological point of view as special reflexes depending upon some difference in the nervous mechanism set into play.

As the flow of saliva is a definite reflex, there should be a definite salivary secretion center. This center has been found, as results of physiological experimentation, to be the medulla oblongata. Owing to the numerous connections of nerve cells in the central nervous system, we should think that this center would

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[3] Pavlov, "The Work of the Digestive Glands", translation by Thompson, London, 1902.

be affected by stimuli from various centers. It is known, however, that the center, and through it the glands, may be called into activity by stimulation of the sensory fibers of the sciatic, splanchnic and vagus nerves. Also, numerous psychical acts, as the thought of juicy and savory food and the feeling of nausea that precedes vomiting, may be accompanied by a flow of saliva, the effect in this case being due probably to stimulation of the secretion center by nervous impulses from the higher nerve centers. The medullary center, however, may be inhibited as well as stimulated. Fear, anxiety or embarrassment produce a parched condition of the throat due to the inhibitory action of nerve impulses arising from the cerebral centers.

a. The Secretory Nerves.

It was in 1857 that the existence of secretory nerve fibers was discovered by Ludwig. This discovery marked the beginning of our knowledge of this particular type of fiber. Ludwig also discovered that a stimulation of the chorda tympani nerve caused a flow of saliva from the submaxillary gland.

It was shown that the salivary glands received a double nerve supply - in part by way of the cervical sympathetic and in part through cerebral nerves. It was seen that not only are secretory fibers carried to the glands by these paths, but that vasomotor fibers are contained in the same nerves, and the arrangement of these vasomotor nerves is such that the cerebral nerves contain vasodilator fibers causing a dilation of the small arteries in the glands and an accelerated blood flow, whereas the sympathetic contains vasoconstrictor fibers whose stimulation causes a constriction of the small arteries of the gland producing a diminished blood flow. The effect of stimulation of these two sets of fibers is somewhat varied in different animals. In the

dog, for instance, it was found that if the chorda tympani nerve is stimulated by weak induction shocks, the gland begins to secrete immediately, and by proper regulation of the stimulation, the secretion may be kept up for hours. This secretion is thin and watery, abundant in amount and contains not more than one or two per cent of the total solids. There occurs at the same time an increased flow of blood through the gland. The gland assumes a redder hue, the veins are distended, and if the veins were to be cut the flow of blood from them would be of a redder hue than that of the passive gland and in addition there is a show of a distinct pulsation which points to a dilation of the small arteries.

If the sympathetic arteries are stimulated, however, different results would ensue. The secretion would be comparatively small in amount; it would be thick and turbid flowing slowly, and containing as much as six per cent of the total solids. The gland at the same time would become pale, and were the veins to be cut, the flow would be slower than from the resting gland, showing that vasoconstriction had occurred.

The increased vascular supply to the gland accompanying the abundant flow of "chorda saliva", and the diminished flow of blood during the scanty secretion of "sympathetic saliva" naturally suggest that the whole process of secretion is a vasomotor phenomenon, the amount of secretion depending only upon the quantity and the flow of the blood through the gland. The idea is an erroneous one, however, as was proved by Ludwig in some of his experiments:

1. He showed that if a mercury manometer is connected with the duct of the submaxillary gland and the chorda is then stimulated for a period of time, the blood-pressure in the duct may become greater

than the blood-pressure in the gland. This proves that the secretion is not derived entirely from the processes of filtration from the blood.

2. If the flow of blood be cut off, entirely from the gland, the stimulation of the chorda tympani still produces a secretion for a short while.

3. If atropine be injected into the gland, stimulation of the chorda tympani causes vascular dilation, but no secretion. Apparently the atropine paralyzes the secretory but not the dilator fibers.

4. Hydrochlorate of quinine injected into the gland causes vascular dilation but no secretion. Here, the secretory fibers are still irritable since stimulation of the chorda tympani produces the usual secretion.

In the gland there is a marked relation of the composition of the secretion to the strength of the stimulus. If the stimulus to the chorda is gradually increased in strength, and the gland is not fatigued, the chemical composition of the secretion is found to change with regard to the relative amount of water, salts and organic material. The water and salts increase in amount with the increase in stimulus up to a certain maximal limit. This effect, strange to say, may be obtained from a perfectly fresh gland as well as from a gland that has been previously secreting actively. The precise results of the organic constituents depend upon the condition of the gland. If previous to the stimulation the gland was in a resting condition, and unfatigued, then the increased strength of stimulus is followed at first by a rise in the percentage of organic constituents. With increased stimulation, however, the increase in organic material soon ceases and finally the amount actually be-

gins to diminish and may fall to a low point in spite of the stronger stimulation.

On the other hand, if the gland at the beginning of the experiment had been previously worked to a great extent, then an increase in the stimulating current may either have no effect at all upon the organic constituents or may cause only a temporary increase followed immediately by a fall.

Having observed many of these facts concerning the factors influencing the secretion of the gland, Heidenhain was led to believe that the conditions determining the secretion of the organic material are different from those controlling the water and salts, and he gave an explanation of the differences in his theory of tropic and secretory nerve fibers."

This theory of Heidenhain supposes that there are two physiological varieties of nerve fibers distributed to the salivary glands. One of these varieties controls the secretion of water and inorganic salts and its fibers may be called "secretory fibers proper", while the other, which is termed "tropic", causes the formation of the organic constituents of the secretion, probably by a direct influence on the metabolism of the cells. If the tropic fibers were to act alone, the organic products would be formed within the cells, but there would be evidence of no secretion. This is the hypothesis which Heidenhain uses to explain the results of the experiment of stimulation of the sympathetic fibers to the parotid of the dog.

The way in which the tropic fibers act leads one to suppose that they set up metabolic changes in the protoplasm of the cells, leading to the formation of certain definite products as mucin and

ptyalin. That these changes involve oxidation is shown by the fact that during activity the gland takes up more oxygen and gives off more carbon dioxide. These gland cells, during their activity, form fresh materials from the nourishment supplied by the blood; that is to say, the anabolic or synthetic processes occur along with the katabolic changes. The katabolic changes are more obvious, however, and are the changes usually associated with the action of the tropic fibers.

At the present time, the theories suggested concerning the method of action of the secretory fibers are merely speculative. Experiments have shown that the amount of water given off by the blood during secretion is somewhat greater than the amount contained in the saliva and the difference between the two can perhaps be accounted for by an increase in the flow of lymph from the gland during activity.

It has been assumed that the effect of the nerve impulse is to cause a splitting up of some simple substance in the cells with a production of an increased number of smaller molecules, whereby the osmotic pressure is increased and a flow of water is set up from the lymph into the cells.

## The Digestive Action of Saliva

The digestive action of saliva is limited to starchy foods. It contains an active enzyme belonging to the group of diastases and this is known as ptyalin or salivary diastase. Its chemical nature is unknown.

According to investigations, the ptyalin as secreted from the gland in some animals, is in an inactive form. Upon coming

into contact with the mucous membrane of the mouth it is converted into active ptyalin by an organic kinase produced in the small buccal glands in the membrane of the cheek and lips. Ptyalin acts readily upon starch converting it into sugar and dextrin, the action being hydrolytic. The hydrolysis, no doubt, takes place in successive stages, for it seems that there are a number of intermediate products formed consisting of a variety of dextrins.

The products of the reaction are probably not absorbed as such. The absorption takes place mainly after the food has reached the small intestine, and before absorption the maltose is acted upon by maltase, the inverting enzyme, and inverted into dextrose the simple sugar. The combined action of ptyalin and maltase is evidently necessary to get the starch into readiness for nutrition. Under the influence of these two enzymes the complex starch molecules are broken up into their constituent elements.

We wonder just how far, under such ordinary circumstances, the salivary digestion affects the starchy foods. The food is chewed in the mouth and mixed with saliva, but the bolus is swallowed much too quickly to allow the ptyalin to complete its action. Recent investigators show that some of the food in a meal remains at the fundic end of the stomach for an hour untouched by the acid secretion. Hence, we are led to believe that salivary digestion is carried on in the stomach to a great extent.

With cooked starch or starch paste the action of the ptyalin takes place more readily than with raw starch. In the latter case, the starch grains are said to be inclosed with a layer of cellulose which resists the action of the ptyalin. In the former case, however, when the starch is boiled, the cellulose layer is de-

stroyed exposing the starch grains within to the action of the enzyme; besides this, the starch has become hydrated, a condition much more favorable for the occurrence of a reaction between it and the enzyme. Hence it is, that we see one of the practical values of cooking vegetable foods.

Besides these chemical functions, the saliva performs other functions which are almost equally as important. By moistening the food the saliva allows free passage of the masticated mass down the oesophagus serving as a lubricator and also at the same time stimulating the taste nerves and exciting the gastric juices in the stomach for later assimilation.

## PART 2.

## THE GASTRIC GLANDS

### Gross Anatomy

Having considered the structure of the salivary glands, their peculiar characteristics and also their digestive action, we shall now deal with the chemical and mechanical changes in the food during its stay in the stomach and the extent to which the products of digestion are absorbed.

The tubular glands that are situated throughout the mucous membranes of the stomach differ in their histological structure and in their secretion in different parts of the stomach. There are two and sometimes three types of glands distinguished, the pyloric, fundic, (and cardiac). Those glands in the pyloric part of the stomach are characterized chiefly by the fact that only one type of gland cell is found in the secreting part of the tubule, the peptic cell, while in the remainder of the stomach, but particularly in the middle or pre-pyloric region, the glands, (fundic glands) are distinguished by the presence of two types of cells, the chief or central cells and the parietal or border cells.

The third type or cardiac glands, is found around the cardia, but its area of distribution varies in different animals, and its histological features are not very definite.

The central cells are said to furnish the digestive enzymes of the stomach, pepsin and rennin, and the parietal cells the hydro-

chloric acid. From a physiological standpoint, it is important to remember that the parietal cells are massed in the glands of the middle or pre-pyloric region of the stomach, that they are scanty in the fundus, and totally absent in the pyloric region. Gutzner called special attention to this relation, and in regard to the differences in movement in these two parts of the stomach, he suggests that normally the bulk of food towards the fundic end of the stomach becomes impregnated with pepsin first; as it slowly moves into the pre-pyloric region, the acid constituent is added. The pyloric glands are said to secrete an alkaline liquid containing pepsin and they form a substance capable of acting as a chemical excitant to the glands secreting the gastric juice. This excitant is called the gastric secretin or "gastric hormone."

## Histological Structure

In regard to the histological structure of the glands, the cardiac glands are said to be of two types: 1) Simple tubules, 2) Small tubulo-racemose glands. The latter are the most common in man; the former occur in considerable numbers in the lower animals.

The secreting tubules of the racemose glands are lined by cells which are grandular in appearance and of a short columnar form, and of the same nature throughout the length of the tubule except near the orifice of the duct where they give place to columnar mucous-secreting cells.

In the glands of the fundus, the tubules are usually rela-

tively long and the duct short. The epithelium of the tubules is composed of two sets of cells, the parietal and central, termed from their relative positions in the tubules.

The central cells are of two types: 1) The type which are not stained with haematoxylin, although their cytoplasm is strongly basophil in aniline-stained sections. The nucleus is spherical and is usually near the middle of the cell. In the resting gland the cytoplasm contains distinct granules most numerous near the inner zone. After a period of activity, the granules diminish in number and the clear outer zone encroaches upon the granular inner zone. It is believed that the granules contain pepsinogen which is converted into pepsin when discharged. Hence, these cells may be appropriately called the peptic cells of the fundic glands.

2) The central cells of the second type are different in appearance and in reactions to stains from those of the first group. They are larger and clearer and are stained blue by Mallory, like mucin-containing cells; whereas, the cytoplasm of the peptic cells is colored yellowish-brown by the reagent. The cytoplasm has no obvious granules; the nucleus is either flattened against the attached end of the cell or wedged into it. This second type of central cell is called the "mucoid."

The parietal cells are a number of large spheroidal or ovoidal cells scattered along the tubule lying between the central cells and the basement membrane. Each of these cells is penetrated by a net-work of minute passages communicating with the lumen of the gland by a fine canal passing between the central cells. They are sometimes present in the neck of the gland or even at the

surface of the stomach. In these places they are wedged in between the ordinary epithelium cells.

In the glands of the pyloric canal, the ducts are longer than those of the fundus glands and the secreting tubules possess cells of only one kind. These are quite similar to the "mucoid" cells of the fundus glands which have flattened basal nuclei. They have an indistinctly-granular appearance and are said to yield pepsin to the gastric juice. They are, however, quite different from the peptic cells of the fundus glands.

### Histological Changes During Secretion

The cells of the gastric glands, especially the central cells show marked changes as a result of a period of prolonged activity. It was found by Heidenhain, after having taken preserved specimens from dogs fed at intervals of twenty-four hours, that in the fasting condition the central cells were large and clear, that during the first six hours of digestion, the central cells as well as the parietal cells increased in size, but that in a second period from the sixth to the fifteenth hour, the central cells became gradually smaller, while the parietal cells remained large or even increased in size. After the fifteenth hour, the central cells increased in size, gradually assuming the condition as held in the fasting condition.

Langley was able to follow the changes in a more satisfactory

way by making observations directly upon living glands. He found that, in the fasting stage, the central cells are charged with granules, and that during digestion the granules are dissolved, disappearing first of all from the base of the cell, which becomes filled with a non-granular material. It has been demonstrated that possibly these granules are the preparatory material for the production of gastric enzymes during the act of secretion. Hence, these granules are oftentimes called the zymogen granules.

## Gastric Secretion

The secretion of the gastric membrane is formed in the small tubular glands distributed over its surface. Obtaining the juice is a difficult procedure since there is no common duct where it may collect in sufficient portions.

Numerous methods were invented for the collecting of the gastric juice or for its analysis, but most of them proved unsatisfactory. A better method of obtaining normal juice was suggested by Beaumont in his famous observations upon Alexis St. Martin. St. Martin, by a premature discharge of his gun, was wounded in the abdomen. Upon healing, a fistula was formed in the abdomenal wall leading to the stomach, so that the contents of the latter could be inspected. Beaumont made numerous interesting experiments upon his patient. Since that time it has become common to make fistulous openings into the stomachs of dogs whenever an examination of the normal juice was necessary.

From the standpoint of experimental investigation, a very important addition was made to our methods by Heidenhain. He showed that a portion of the stomach, the pyloric for instance, might be cut away from the rest of the organ and be given artificial opening to the exterior, whence the gastric secretion may be obtained and examined as to its properties.

The normal gastric secretion is a thin, colorless liquid with a strong acid reaction and a characteristic odor. Its specific gravity is variable, but the average is about 1.002. Upon analysis it is found to contain mucin, protein and inorganic salts, but the chief constituents are, hydrochloric acid, and possibly the enzymes, pepsin, rennin, and lipase. In dogs, according to Rosemann, the secretion has a specific gravity of 1.002 to 1.004 and contains .4277 per cent of dry material of which .1325 per cent is ash. Upon analysis of the ash, it was found to contain 24 per cent potassium, 19 per cent sodium, and .18 per cent of calcium. The hydrochloric acid amounts to .55 per cent. Rosemann stated that during a secretion that lasted for three and one quarter hours in one animal, about 5 grams of chlorin were given off in the secretion in the form of chlorids, an amount which is equal to that contained in the entire blood.

The one most outstanding and interesting feature of the gastric juice is the manner in which it withstands putrefaction. It may be kept for months at a time without becoming putrid and with very little change, if any, in its total acidity. This characteristic which it possesses shows it to have antiseptic properties,

which fact is attributed to the presence of the free acid.

### a. Nature of the Acid

The nature of the free acid in the gastric juice was previously the subject of dispute, some contending that the acidity was due to the presence of hydrochloric acid, while others, that an organic acid, called "lactic acid", was present in the secretion. Recent investigators have proved that the acidity is due to the hydrochloric acid. Schmidt first demonstrated satisfactorily by analysis that, if in a given specimen of gastric juice, the chlorid were all precipitated by silver nitrate and the total amount of chlorin determined, it was found that there was more chlorin present than could be held in combination by the bases in the secretion. Apparently, some of the chlorin must have been in combination with hydrogen as hydrochloric acid. The percentage of hydorchloric acid in the gastric juice as it is obtained from a fundic sac in the stomach varies from .4 to .5 per cent; this supposedly represents the concentration of the acid in the juice as it is secreted.

The acidity of the contents of a normal stomach during digestion was found to be much lower, varying around .2 per cent as a maximum. This low acidity may be accounted for partially by dilution, the neutralization from the alkaline salts of the saliva or the gastric mucosa, or by combination of the protein in the food, but it is reduced mainly by the regurgitation of the alkalin duodenal contents which occurs periodically during digestion. It is maintained that this regurgitation is a self-regulating mechan-

ism for maintaining a low acidity of the gastric contents.

A distinction is made by clinicians between the free and combined acid in the gastric secretion. By free acid is meant that the acid exists in solution and is, therefore, largely dissociated with the production of a corresponding amount of hydrogen ions. By the term "combined" acid is meant the acid which in some way is combined with the protein material. In this form the acid is less dissociated and the acidity or the concentration of hydrogen ions is less. It is preferable to abandon the use of the terms free and combined acid for physiological purposes, and instead to express the degree of acidity in terms of the actual hydrogen ion concentration as the activity of the pepsin is controlled by this.

Experiments show that an acidity as high as one tenth normal, which concentration was given the secretion by some investigators, is not favorable to the digestive action of pepsin, and as a matter of fact, it is found that in ordinary digestion the acidity of the stomach contents is always lower. We can reasonably assume that this reduction in the acidity is not a matter of chance but a properly regulated adaptation to ensure the most favorable conditions.

### b. Origin of Hydorchloric Acid

The fact that the acid of the gastric juice is a mineral acid possessing considerable strength, has excited much interest. Many attempts have been made to discover the histological elements concerned in the secretion and the nature of the chemical reaction

by which it is produced.

In regard to the histological elements which enter into the secretion, it was first believed that the parietal cells of the gastric tubules constitute the acid secreting cells. This belief was founded upon the fact that in the region where these cells were present, the secretion is distinctly acid, and where they are absent or few in number, the secretion is alkaline or less acid. For instance, in the pyloric region these cells are lacking and the secretion is alkaline. By microchemical reactions it was clearly seen that the parietal cells are particularly rich in chlorids, and this fact serves to associate them with the production of the acid. It appears evident that the hydrochloric acid must, in the long run, be formed from the chlorids in the blood. The chief chlorid is sodium chlorid, and by some means this compound is broken up; the chlorine is combined with hydrogen and is then distributed upon the surface of the stomach as hydrochloric acid. To support this fact, it has been shown that if the chlorids in the blood are reduced by eliminating them from the food for a time, the gastric secretion no longer contains acid. However, upon the addition of sodium bromide or potassium iodide to the food, there is brought about the formation of hydrogen bromide and hydrogen iodide, together with hydrochloric acid in the gastric juice. Maly has suggested that acid phosphates may be produced in the first instance, and then by reacting with the sodium chlorid may produce hydrochloric acid according to the formula:

$Na\ H_2PO_4 + NaCl \rightarrow Na_2HPO_4 + HCL$.

Other theories have been proposed, but no explanation of the details of this reaction is satisfactory. Many attempts have been made on the part of numerous observers to determine, by microchemical methods, the exact point in the gastric glands at which the acid is formed. Harvey and Bensley, by making use of dyes, state that the free acid is found only on the internal surface of the stomach or in the neck of the glands. These observers advance the hypothesis, then, that the parietal cells secrete a chlorid of an organic base, and this compound, in some way, yields free hydrochloric acid only after it reaches the mouth of the gland. While the ultimate source of the chlorine of the hydrochloric acid is to be found in the neutral chlorids of the blood certain intermediate compounds are formed within the parietal cells from which the acid is eventually produced.

## Normal Mechanism of the Secretion

It has usually been assumed that the gastric glands are quiescent when the stomach is empty and are stimulated to activity during the eating and digestion of food. According to Carlson, this view is not wholly correct. Even in the period of fasting there is a small, continuous secretion varying from 2 to 50 c.c. per hour. During the act of eating, however, and throughout the period of digestion, the rate of secretion is greatly increased reaching a flow of as much as 3.5 c.c. per minute.

The present-day explanation of the origin, maintenance and regulation of the flow of secretion is chiefly due to the efforts

of Pavlov. He disrupted the former theory of gastric secretion by showing that mechanical stimulation of the gastric mucous membrane has no effect on the secretion of the tubules.

In an ordinary meal, the secretion is first caused to flow by the sensations of eating, - a psychical secretion. The afferent stimuli originate in the mouth and nostrils; the efferent path is through the vagus nerve. This reflex insures, at least, the beginning of gastric digestion, but its effect is further completed by action in the stomach itself. Certain foods, it seems, contain substances designated as "secretagogues", that are able to bring about a secretion of gastric juice when taken into the stomach. Hence, meat extracts and juices, soups, etc. are particularly effective in this respect. Milk and water cause less secretion. In certain common articles of food, such as bread and white of eggs, these ready-formed "secretagogues" are lacking and they have no effect of this kind at all. If they are introduced into the stomach of a dog through a fistulous opening in order not to arouse a psychical secretion, as for example, when the animal is sleeping, they cause no flow of gastric juice and are not digested. When such articles are eaten, however, they cause a psychical secretion, and when this has acted upon the foods, some products of their digestion in turn arouse a further flow of gastric juice.

The mechanism of secretion, then, takes place in three steps: 1) The psychical secretion or appetite secretion. 2) The secretion from "secretagogues" contained in the food. 3) The se-

cretagogues secretion contained in the products of digestion.

It cannot be stated positively the manner in which the secretagogues act. As the gastric glands possess secretory nerve fibers, the first suggestion offering itself is that the secretagogues, by acting on the sensory fibers in the gastric mucous membrane, reflexly stimulate the secretory fibers. This explanation, however, has been rendered untenable by the fact that the effect of these substances has been obtained after complete severance of the nervous connections of the stomach. If this so-called chemical secretion, then, is produced by a nervous reflex, the nerve centers concerned must lie in the stomach itself, the reflex must take place through the intrinsic ganglion cells.

Another explanation of the action of the secretagogues has been offered by Edkins, showing that decoctions of the pyloric mucous membrane made by boiling in water, acid, or peptone solutions, when injected into the blood, cause a marked secretion of gastric juice. These substances, when injected alone into the blood, cause no such effect, and decoctions of the mucous membrane of the fundic end of the stomach are without action on the gastric secretion. Edkins, therefore, suggests that the secretagogues, whether preformed in the food or formed during digestion, act upon the pyloric mucous membrane and form a substance which he designates as "gastrin" or "gastric secretin", and this substance after absorption into the blood, is carried to the gastric glands and stimulates them to secretion.

The effect, then, is not a reflex of the usual nervous type,

but an instance of the stimulation of one organ by chemical products formed in another. [4]Starling has emphasized the fact that this mode of control is frequently employed in the body. He proposes to designate such substances by the general term of "hormones". The specificity of its origin and the fact that it acts upon the pancreas as well as the gastric glands, has caused some observers to doubt whether the part it plays is exactly that as described by Edkins. The chemical nature of it has not been determined definitely, but it seems to be a basic body containing an imidazol grouping and related in structure to histamine.

It is important to emphasize the fact that in the normal secretion of gastric juice, i.e. in the secretion which takes place during an ordinary meal, we must distinguish between an nervous secretion due to the action of the secretory nerves in the vagus, and a chemical secretion which is due to the chemical stimulation of the secretagogues or of the hormones produced by them.

According to the researches of Pavlov and his co-workers, there seems to be an indication that the quantity and properties of the secretion vary with the character of the food. Other conditions being the same, the quantity of the secretion varies with the amount of food to be digested, and so far as the psychical or appetite secretion is concerned, with the palatableness of the food. Different kinds of food produce secretions varying not only as regards quantity but also in their acidity and digestive action. The secretion produced by bread, though less in quantity than that caused by meat, has a greater digestive action. On a given diet,

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[4] Starling - "Recent Advances in the Physiology of Digestion." 1906.

the secretion assumes certain characteristics, and Pavlov is further convinced that further work will disclose the fact that the secretion of the stomach is not caused normally by general stimuli all affecting it alike, but by specific stimuli contained in the food or produced during digestion, whose action is of such a kind as to arouse reflexly the secretion best adapted to the food ingested.

Fig. 6 represents a chart on which is plotted the variation in quantity of gastric secretion in a dog after a mixed meal; there is shown also the variation in acidity and in digestive power.

One of the curves shows the effect of a mixed diet of 600 c.c. of milk, 100 gms. of meat, and 100 gms. of bread upon the gastric secretion. It will be

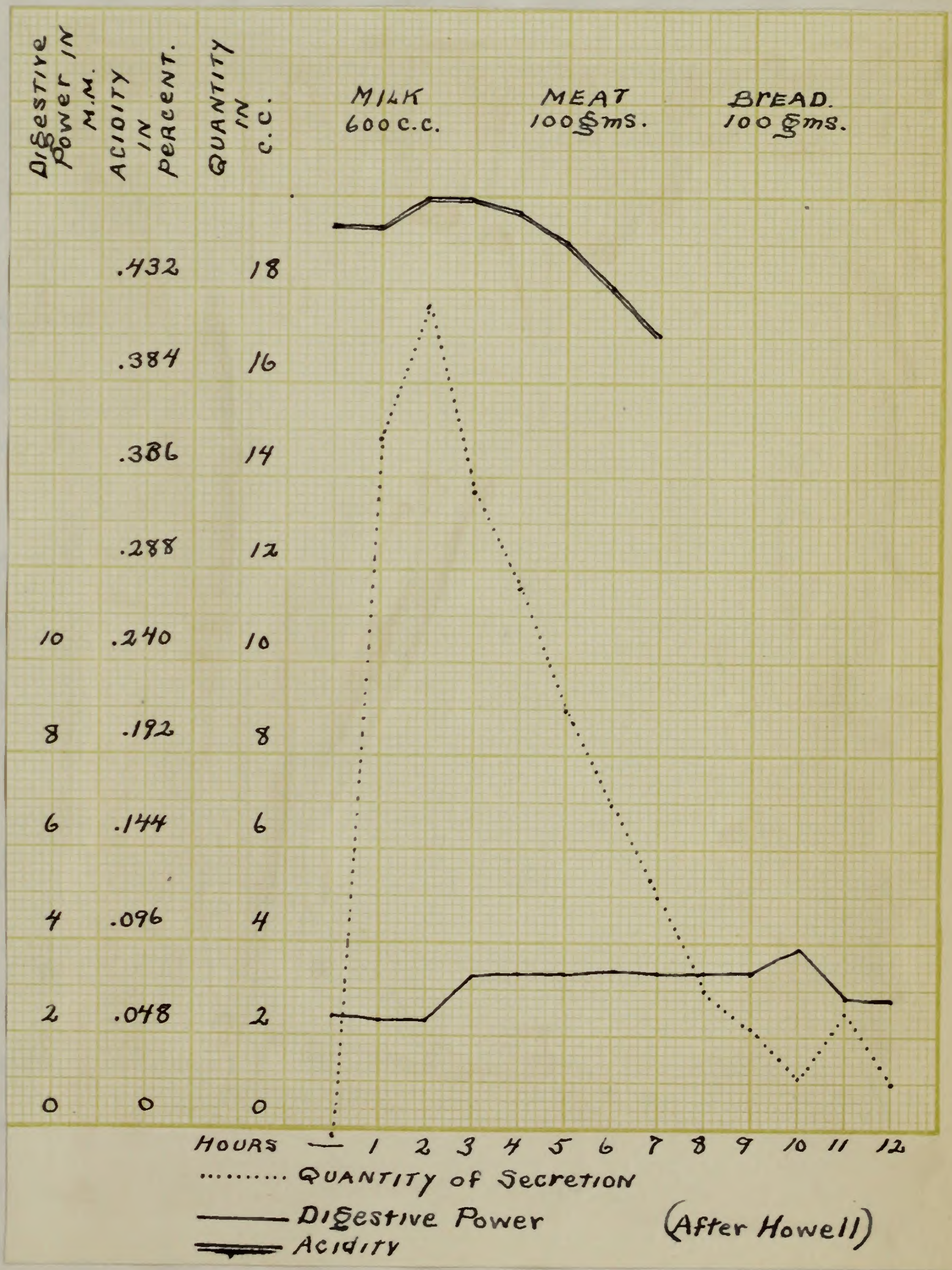

Fig. 6.

noticed that the secretion began shortly after the ingestion of the food, and increased rapidly to a maximum that was reached in two hours. After the second hour, the flow decreased rapidly and uniformly to about the tenth hour. The acidity rose slightly between the first and second hours, and then fell gradually. The digestive power showed an increase between the second and third hours.

## Secretory Nerves of the Gastric Glands

Pavlov first demonstrated that the secretion of the gastric juice is under the control of the nervous system and that the secretory fibers are contained in the vagus. When a direct stimulation is brought to the peripheral end of a cut vagus, there is caused a secretion of the gastric juice after a long, latent period of several minutes. This latency may be due possibly to the presence in the vagus of inhibitory fibers to the gland which, stimulated simultaneously with the secretory fibers, delay the action of the latter.

A striking proof of the fact that the secretion is due to the action of vagus fibers is furnished by such an experiment as was performed by Pavlov. He divided the oesophagus in the neck and brought the two ends to the skin in order to make separate fistulous openings to the exterior. Under these conditions, when the animal ate and swallowed food, it was discharged to the exterior instead of entering the stomach. The animal thus had the enjoyment of eating without actually filling the stomach. Eating

in this style forms what the author called a "fictitious or sham meal". It was found that it causes an abundant flow of gastric juice as long as the vagi are intact, but has no effect upon the secretion when these nerves are cut. Evidently then, the sensations of taste, odor, etc. developed during the mastication and swallowing of food, set up reflexly a stimulation of secretory fibers in the vagus. Pavlov calls a secretion produced in this way a "psychical secretion", a term which implies that the reflex must be attended by conscious sensations. Other observers, as Carlson, designate this form of secretion as the "appetite secretion". In favorable cases, the fictitious feeding has been continued for five or six hours and a large amount of gastric juice has been collected from a fistula, although no food actually entered the stomach. The psychical secretion, it was found, once started, may continue for a long time after the stimuli have ceased, and it was also found to be of the same chemical composition as that produced when the food enters the stomach.

## The Gastric Digestive Enzymes

a. Pepsin

Pepsin is a proteolytic enzyme that exhibits the peculiarity of acting only in an acid media; therefore, peptic digestion in the stomach is the result of the combined action of pepsin and hydrochloric acid. Pepsin is influenced in its action by temperature, as are other enxymes, low temperatures retarding its action and sometimes even suspending it, while a high temperature will increase it. The maximum temperature is stated to be from 37° C. to

40° C., while exposure for some time to 80° C. results in the total destruction of the enzyme.

Laboratory preparations of pepsin are made conveniently by mincing thoroughly the gastric mucous membrane and then extracting for a long time with glycerin. Purer preparations of pepsin are made by what is known as the "Brucke's method" in which the mucous membrane is minced and is then self-digested with a 5 per cent solution of phosphoric acid. The phosphoric acid is precipitated by the addition of lime water, and the pepsin is carried down in the precipitate. The precipitate, after being washed, is carried into solution by dilute hydrochloric acid and a solution of cholesterin in alcohol and ether is added. The cholesterin is precipitated and, as before, carries down with it the pepsin. This precipitate is collected, washed carefully, and then treated repeatedly with ether, which dissolves and removes the cholesterin leaving the pepsin in aequous solution. This method is interesting not only because it produces a pure form of pepsin but also in that it illustrates one of the properties of enzymes, viz. the readiness with which they are absorbed by precipitates in their solutions.

It is supposed that pepsin is formed in the central cells of the gastric tubules, but is present in the cells as a zymogen or propepsin which is not changed to the active pepsin until after secretion. The propepsin can be readily extracted from the mucous membrane, and since it is known that the zymogen is converted quickly into active pepsin by the action of the acids, it is obvious that in the normal gastric juice the existence of the

hydrochloric acid insures that all the pepsin shall be present in active form.

b. Rennin

The characteristic possessed by the calf's stomach of curdling milk has been known, from remote times. This action takes place with remarkable rapidity under favorable conditions, a large mass of milk setting to a firm coagulum within a short period of time. It has been shown that this effect is due to an enzyme called "rennin" or "rennet". The rennin, like the pepsin, is supposed to be formed in the chief cells of the gastric tubules and to be present in the glands in a zymogen form, the prorennin or "prochymosin", which after the secretion is converted into the active enzyme. This conversion takes place readily under the influence of acid. Rennin may be obtained easily from the mucous membrane of the stomach by extracting with glycerin or water, or by digesting with dilute acid. Good rennin extracts cause the milk to clot with great rapidity at a temperature of 40 C.; the time of clotting is said to vary inversely as the amount of rennin, or the product of the amount of rennin and the time necessary for clotting is a constant. The curdling of milk involves two independent processes: first, the rennin acts upon the casein in the milk and converts it into a substance known as "paracasein". The paracasein then reacts with the calcium salts of the milk, forming an insoluble protein which constitutes the curd or coagulum. What takes place when the casein is converted to paracasein is not understood. Some physiologists have regarded the change as a cleavage process although this view has been denied by others. Others have supposed that a trans-

formation or rearrangement of molecular structure occurs. The differences, however, in properties between casein and paracasein are not great, the most marked difference being that the latter, in presence of calcium salts, gives an insoluble coagulum. If soluble calcium salts are removed from milk by oxalate solutions, the milk does not curdle upon the addition of rennin. The addition of lime salts restores this property. Casein is also precipitated from milk by an addition of an excess of acid. When milk stands for some time, the action of bacteria upon the milk-sugar leads to the formation of lactic acid; when this acid reaches a certain concentration, it causes a precipitation of the casein.

The action of rennin is confined to milk so far as positive knowledge of it is concerned. Casein is the chief protein constituent of milk and has, therefore, an important nutritive value. The value of the curdling action is not at once apparent, but we may assume that casein is more easily digested under the conditions that exist in the body after it has been brought to a solid form, or perhaps the coagulation of the casein insures that it will be retained in the stomach and be submitted to gastric digestion instead of being ejected promptly into the duodenum as occurs with liquids. The action of rennin goes no further than the curdling; the digestion of the curd or coagulum is carried on by the pepsin, and later by trypsin in the intestines, as in the case of other proteins.

(Sequel)

These gastric digestive enzymes are unequally distributed in different animals and undergo changes in their potency even in the same animal. We find that rennin is especially profuse in the stomachs of suckling animals, and that its amount gradually diminishes as the animals mature. Its place is then taken by the pepsin which acts in an acid medium at a time when the adult stomach is capable of more resistance than it had a short while after birth.

## Digestive Changes in the Stomach

It is probable that the ptyalin swallowed with the food continues to exert its action upon the starchy material in the fundus for a long time so that in this way the starch digestion in the stomach may be important. In regard to the fats, it is usually believed that they undergo no truly digestive change in the stomach. They are set free from their mixture with other food-stuffs by the dissolving action of the gastric juice upon proteins, they are liquified by the heat of the body, and they are disseminated through the chyme in a coarse emulsion by the movements of the stomach. In this way they are mechanically prepared so that the subsequent action of the pancreatic juice is much favored. Some observers[5] have stated that the gastric juice normally contains a lipase capable of bringing about a hydrolytic cleavage of the neutral fat into glycerin and fatty acids. It would appear, however, that this lipase is readily destroyed by an acidity of .2 per cent. hydrochloric acid, so that, if it is of functional importance in gastric digestion, its action, like that of ptyalin, must be confined to the early period of digestion before the con-

[5] Hall and Keeton,"Journal of Biological Chemistry",1917,32,127.

tents of the stomach have reached their normal acidity.

Concerning proteins, the point of interest is as to how far they are digested during their stay in the stomach. The extent of digestion varies under different circumstances; with the consistency of the food, the duration of the stay in the stomach, etc. In some experiments, it is stated that 48 per cent. of a given amount of protein passed through the pylorus as peptones and proteoses, about 20 per cent. entered the intestine undigested, and 20 to 30 per cent. absorbed from the stomach.* In the liquid chyme forced through the pylorus into the duodenum, one may find unchanged proteins, primary or secondary proteoses, peptones or possibly cleavage products beyond this stage. It is stated, however, that most of the material is in the form of proteoses.

The true value of peptic digestion is not so much in its own action as in its combined action with the trypsin, or the trypsin and eripsin found in the intestine. The preparatory digestion in the stomach is important as regards protein foods from several standpoints: first of all, in regard to the mechanical preparation of the food and its discharge in convenient quantities easily handled by the duodenum. Secondly, in the more or less complete hydrolysis to peptones and proteoses, whereby, the subsequent action of the proteolytic enzymes of the intestines may be accelerated. In some cases, this preliminary action of the pepsin - hydrochloric acid may be quite necessary. Native proteins, as serum albumin are not acted upon by the trypsin, but, if subjected to the action of pepsin-hydrochloric acid, they are easily digested by this enzyme. These facts seem to indicate that the peptic digestion is not so much an end in itself as a preparation for sub-

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* This matter is further discussed on page 43.

sequent intestinal digestion. Therefore, it is possible to remove the stomach without producing fatal results. The oesophagus may be stitched to the duodenum and the animal may continue to live normally. Special precautions, however, are necessary in the matter of feeding.

### a. Pepsin-hydrochloric Acid Digestion

It has long been known that solid proteins, when exposed to the action of normal or artificial gastric juice, swell up and pass into solution. This soluble protein was known not to be coaguable by heat, and was remarkable in its being more diffusible than other forms of soluble proteins. This end-product of digestion was formerly thought of as a soluble protein with properties fitting it for quick absorption, and to it was given the name "peptone". The process, however, is complicated. In the conversion to the peptone, so-called, the protein under digestion passes through a number of intermediate stages. These intermediate stages were partly isolated, and were given specific names, as "acid-albumin", "parapeptone", and "propeptone". The first step is the conversion of the protein to an acid albumin. This change may be considered as being chiefly an effect of the hydrochloric acid, yet in some way the combined action of the pepsin - hydrochloric acid compound is more effective than a solution of acid alone of the same strength. Like the acid albumins, the syntonin is readily precipitated on neutralization. In the beginning of the peptic digestion, then, if the solution is neutralized with dilute alkali, there occurs an abundant precipitation of syntonin. Later on in the digestion, neutralization gives no such effect - the syntonin has all passed to a further stage of digestion. Under the influ-

ence of the pepsin, the syntonin undergoes hydrolysis with the production of a number of bodies which, as a group, are called "primary proteoses" or "protalbumoses".

Though several numbers of this group have been isolated and given distinct names, so much doubt prevails as regards their chemical nature, that it is best perhaps to regard them as a group of compounds which under the continued influence of the pepsin undergo still further hydrolysis and form the secondary proteoses or "deutero-albumoses". Compared with the primary proteoses, the secondary ones are distinguished by a greater solubility; they require a stronger saturation of the neutral salts to precipitate them. The secondary proteoses undergo still further hydrolysis with the production of peptone. Hence, we can readily see that the several stages in peptic digestion are represented as following in sequence.

It is the opinion of many authors that even in the beginning of the digestion the protein molecule may be split up into several complexes and that some of the end-products are formed early in the action. The end-result of the action of pepsin in the stomach is the conversion of more or less of the protein of the food into simpler and more soluble peptones and proteoses. The action of the pepsin enzyme is a preparation for the more complete hydrolysis that takes place in the intestine under the influence of trypsin. While it is a relatively weak proteolytic enzyme, it plays an important part in bringing about the splitting up of the protein molecule, and its value in this regard is increased by the fact that it is adapted to act upon proteins of all kinds and bring them to a stage suitable for the more complete action of the proteolytic enzymes of the intestine.

## Absorption in the Stomach

It is possible that, in the stomach, there may be an absorption of the water, salts, sugars, dextrins, that may have been formed in salivary digestion from starch or that may have been eaten as such. Besides this, absorption may occur of soluble or liquid substances such as drugs or alcohol that have been swallowed.

It was formerly thought that the stomach absorbs easily such things as water, salts, peptones and sugars. Actual experimentation, however, has shown, under conditions as normal as possible, that absorption does not take place readily in the stomach - certainly not as easily as it does in the intestines. The methods for performing the experiments have varied, but best results have been obtained by establishing a fistula of the duodenum just beyond the pylorus of the stomach. This type of experiment shows that water, when taken alone, is practically not absorbed at all in the stomach. Von Mering's[6] experiments of this nature show that as soon as water is introduced into the stomach, it begins to pass into the intestine, forced out in a series of spurts by the contractions of the stomach. Within a comparatively short while practically all the water can be recovered in this way, none or very little having been absorbed in the stomach. As an example, in a large dog with a fistula in the duodenum, 500 c.c. of water were given through the mouth. Within 25 minutes, 495 c.c. had been forced out of the stomach through the duodenal fistula. This result is not true for all liquids, however; alcohol, for example, is readily absorbed.

The absorption of salts in the stomach has not been thorough-

[6] Von Mering in Edkin's "Journal of Physiology", 13, 445, 1892.

ly investigated. Sodium iodide is absorbed very slowly or not at all in dilute solutions. Its absorption does not become important until its solutions reach a concentration of 3 per cent. or more. This result, if applicable to all soluble inorganic salts, would indicate that under normal conditions they are practically not absorbed in the stomach, since it is not supposed that they are normally swallowed in solutions as concentrated as 3 per cent. The absorption of sodium iodide is said to be very much facilitated by the use of condiments such as mustard, pepper or alcohol which act either by causing a greater congestion of the mucous membrane or by directly stimulating the epithelial cells.

In regard to the sugars, the experiments of Von Mering indicate that though absorption takes place, it is not rapid nor marked unless the solutions are quite concentrated; we may infer, therefore, that in an ordinary meal the sugar formed from the starchy foods by the action of ptyalin is passed on to the intestine for further digestion and absorption.

The fact whether or not digested proteins are absorbed from the stomach has been a matter of controversy. Some of the older experimenters stated that as much as 20 to 30 per cent. of the protein of a meal might be absorbed in the stomach, but the results of more recent work, on the contrary, show that little or no absorption takes place in the stomach under normal conditions. When a definite amount of protein was introduced into the stomach of an experimental animal, it could all be recovered, as estimated by nitrogen determinations from a duodenal fistula.

Fats, as we have seen, undergo no digestive changes in the stomach. The processes of saponification and emulsification are as-

sumed to be preliminary steps to absorption and these processes usually take place after the fats have reached the small intestine.

# PART 3.

# THE LIVER

## Gross Anatomy

The liver is the largest gland in the body weighing from 1,400 to 1,700 grams. It is situated in the upper part of the abdominal cavity rather more on the right than on the left side and immediately below the diaphram into the concavity of which its upper part fits, and reaches across the middle line above the pyloric end of the stomach. A deep fissure incompletely divides the organ into right and left lobes of which the right is much larger; on its under surface, shallow grooves mark off several minor lobes. The upper surface is smooth and convex. The vessels carrying blood to the liver are the portal vein and the hepatic artery. Both enter it at a fissure on its under side called the "portal fissure", and there also a duct passes out from each half of the organ. The ducts unite to form the hepatic duct which meets at an acute angle the cystic duct proceeding from the gall-bladder which is a pear-shaped sac in which the bile or gall, as it is commonly called, formed by the liver, accumulates when the food is not being digested in the intestine. The common bile duct formed by the union of the hepatic and cystic ducts, opens into the duodenum.

The liver plays an important part in the general nutrition of the body. Its functions are many but on the whole they depend upon the properties of the liver cell which constitutes the physio-

logical and anatomical unit of the organ. These cells are seemingly uniform in structure throughout the whole substance of the liver, but a clear idea of their anatomical relations to one another and to the blood vessels, lymphatics and bile ducts must be obtained in order to understand clearly the different functions they fulfill. Each lobule is supplied with blood coming in part from the portal vein and in part from the hepatic artery. The blood from the former source contains the soluble material absorbed from the alimentary canal, as sugars and amino-acids, the split products of protein. These absorbed products are submitted to the metabolic activity of the liver cells before reaching the general circulation. Besides this, each lobule gives origin to the bile capillaries which arise between the separate cells and which carry off the bile formed or secreted within the cells.

## Histological Structure

The liver is compound tubular in structure. It is surrounded by a sheath of white fibrous tissue, called the "capsule of Glisson", which is covered by the peritoneum. On the under surface of the gland the capsule follows the blood vessels at the portal or transverse fissure into the gland, and forms the interlobular connective tissue and interlobular reticulum.

The liver is divided into lobes and lobules, of which the latter represent the units. Each lobule is about 1 mm. in diameter, and it is estimated that there are about 480,000 in the

liver. Each consists of anastomosing and radiating chains of hepatic cells, the tubules, that start from the central or interlobular vein which represents a large sinusoid. These chains are separated from one another by reticulum, which supports the cells and the interlobular blood capillaries; these capillaries are of the sinusoidal variety; i.e. the endothelium is attached to the epithelium of the tubules. As a result, the material for secretion is transferred directly from the cells to the blood without the intervention of the lymph or lymph vessels.

The hepatic cells are large mononuclear masses of protoplasm; occasionally two nuclei may be present in one cell. The cytoplasm is finely granular and an exoplasmic zone may be differentiated. These cells are traversed by a net-work of fine canals, the secretory capillaries, that may communicate with the bile capillaries between the cells, or, on the other hand, with the sinusoidal blood capillaries that surround the epithelial cells. It has been shown that these capillaries extend to the periphery of the hepatic cell and are in such close relation with the sinusoidal that the internal secretions of the liver, from its glycogenic and urea-forming functions, are readily poured into the blood vessels.

A few fat globules are normal in hepatic cells; these are usually small in size and are distributed mainly in those cells at the periphery of the lobule. After a meal rich in fatty foods, the number of fat globules is greatly increased. The fat globules usually coalesce to form large droplets and the condition is that of fatty "infiltration". In fatty degeneration of the liver, the fat globules are numerous but small in the degenerating cells and they do not coalesce.

## The Secretion of the Bile

Several experiments have been performed to ascertain whether or not the secretion of the bile is controlled by a special set of secretory fibers. The secretion itself is continuous but varies in amount under different conditions. It has been shown that stimulation of the spinal cord or splanchnic nerve diminishes the flow of bile, while section of the splanchnic branches may cause an increased flow. The splanchnics carry vasomotor nerves to the liver and stimulation or section of these nerves will, therefore, alter the circulation in the organ. It is believed that no special secretory nerve fibers exist since the secretion increases and decreases with the blood-flow. The metabolic processes in the liver cells which produce the secretion, no doubt, go on continually, but they are increased with the blood-flow. We may believe, then, that the quantity of the bile secretion varies with the quantity and composition of the blood flowing through the liver, and that normally the blood contains chemical substances which stimulate the liver cells to secrete bile.

It has been stated on the basis of experimental evidence that when the supply of portal blood is cut off, the amount of bile formed is greatly reduced, and that, therefore, it is possible that the substances from which the bile is formed or which serve to stimulate the production of bile, are furnished chiefly by the portal blood. These substances are called "cholagogues". The therapeutical agents which are capable of giving this action are still a subject of controversy. On the physiological side the

following facts have been accepted: Any agent that causes an hemolysis or destruction of red corpuscles increases the flow of the bile, or the same effect is produced if a solution of haemoglobin is injected directly into the blood. When fed or injected directly into the blood, bile causes an undoubtable increase in the secretion. This effect is due to the effects of both bile acids and bile pigments. As the bile acids have a hemolytic effect upon red corpuscles, it might be assumed that their action as cholagogues is due indirectly to this feature.

Lastly, there is evidence that there is a secretion similar to that acting upon the pancreas which exerts an effect upon the secretion of bile. When acids (.5 per cent HCL) are injected into the duodenum or upper part of the jejunum, the secretion of bile is increased; since this effect takes place when the nervous connections are severed, the effect is explained by assuming that the acid converts prosecretin to secretin, and the latter, after absorption into the blood, acts upon the liver cells.[7]

The same type of reaction may be obtained by injecting secretin into the blood supply directly. Since it is a normal function of the stomach during a meal to inject acid chyme into the duodenum, the importance of this secretin reaction in adapting the secretion of bile to the period of digestion is evident.

### a. Formation of Bile

As has been stated, bile is secreted continuously but not at a uniform rate, however. This variation in the secretion is dependent upon intermittent stimuli as results whenever the stom-

[7] Falloise in Maly's "Jahres-bericht der Thier-chemie", 33, 611, 1904.

ach ejects its contents into the duodenum. This shows that the hepatic cells are under control of a mechanism which regulates their activity. It may be assumed, then, that the liver possesses secretory fibers arising in the celiac ganglion and reach the organ by way of the hepatic plexus. However, since a reflex contraction of the gall-bladder and a more copious flow of bile may be brought about by the introduction of an acid into the duodenum, and since these effects may also be obtained after the liver has been isolated from the nervous system by cutting the nerves, it has been concluded that the secretion of bile is regulated by a definite hormone.

Starling recognizes in the stimulant the secretion of the duodenal mucosa, basing his statement upon the fact that the injection of this agent into the blood-stream brings about a copious flow of bile.

Inasmuch as the hepatic cells derive the material from which they form the bile from the portal vein, their activities must be adjusted to a very low secretory pressure. It has been shown by Burton-Opitz[8] that the blood arrives in the tributaries of the portal system of the dog under a pressure of about 12 m.m. Hg., and enters the hylum of the liver under a pressure of 9 m.m. Hg. Since the pressure of the inferior vena cava opposite the orifices of the hepatic veins is practically zero, a pressure of about 9 m.m. Hg. must suffice to push the blood through the portal terminals. This is the pressure under which the hepatic cells perform their function. The blood of the hepatic artery, on the other hand, arrives

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[8] "Quart. Journal of Experimental Physiology," vii. 1913, 57.

at the liver, say, under a pressure of 100 m.m. Hg. which pressure is largely used up in overcoming the resistance at the interstitial capillaries. Both types of blood then traverse the interlobular veins, that of the portal vein furnishing the secretory material and that of the hepatic artery, the oxygen.

It should be noted that the formation of the bile takes place in accordance with the same principles as do the other secretions. It is not only due to filtration but also to osmosis, diffusion and vital activity on the part of the hepatic cells. As a proof of this it may be shown that these cells are able to secrete against a higher pressure than the portal blood pressure. If a cannula is inserted into the common bile duct which in turn is connected with a narrow, verticle glass tube, the bile will rise in the tube until it reaches a point where its height equals a pressure considerably more than is found in the portal vein at the hilum of the liver. The rapidity with which this level is reached depends upon the general condition of the animal. In a robust cat under ether, 30 to 60 minutes are required before the pressure in the common duct will have risen to 15 m.m. Hg. a pressure equal to twice that found in the portal vein of the animal.

Since, then, the hepatic cells are able to secrete against a higher pressure than that in which they obtain their material, filtration evidently is not the only factor concerned in the processes.

### b. Composition of Bile

From a physiological standpoint, bile is partly an excretion

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carrying away certain waste products, and partly a digestive secretion playing an important role in the absorption of fats and possibly in other ways.

Chemical analysis of bile has shown that, in addition to water and salts, it contains bile pigments, bile acids, cholesterin, lecithin, neutral fats and soaps, occasionally a trace of urea, and a mucilaginous nucleo-albumin formerly designated as "mucin". This last mentioned is not formed in the liver cells but is added to the bile by the mucous membrane of the bile ducts and gall-bladder. The quantity of these substances present in the bile varies in different animals and under different conditions.

Bile, according to the animal from which it is derived or obtained, contains one or the other or a mixture of the two pigments, bilirubin and biliverdin.

Bilirubin stands to biliverdin in the relation of an oxidation product. The formula given to bilirubin is $C_{32}H_{36}N_4O_6$ and biliverdin $C_{32}H_{36}N_4O_8$, the latter being prepared readily from the former by oxidation. These pigments give a characteristic reaction known as "Gmelin's reaction" with nitric acid containing some nitrous acid. If a drop of bile be brought into contact with a drop of nitric acid the bile undergoes a succession of color changes, the order being, green, blue, violet, red and a reddish yellow. The play of colors is due to successive oxidations of the bile pigments; starting with bilirubin, the first stage is due to the formation of biliverdin.

The bile pigments originate from haemoglobin. This origin was first indicated by the fact that in old blood clots there was

found a crystalline product, the so-called "haematoidin" which was undoubtedly derived from the haemoglobin, and which upon more careful examination was proved to be identical with bilirubin. This origin is now universally accepted. It is supposed that when the blood corpuscles disintegrate, the haemoglobin is brought to the liver, and there, under the influence of the liver cells, is converted to an iron-free compound, bilirubin or biliverdin.

The bilirubin is formed from the hematin of the haemoglobin by a process which involves the splitting off of its iron. It is very significant that the iron separated by this means from the hematin is held back in the liver for the most part, a very small portion being secreted in the bile. It seems probable that the iron held back in the liver is again held in some way to make new haemoglobin in the so-called "haematopoietic" organs.

There is a conspicuous lack of quantitative data in regard to the amount of bile pigment secreted daily. Owing to the lack of satisfactory method of estimating this substance, its percentage in the bile, as given by different authors, varies from .04 per cent to .25 per cent. The bile pigments are carried in the bile to the duodenum and are mixed with the food in its passage through the intestine. Under normal conditions, neither bilirubin nor biliverdin occurs in the feces, but in their place is found a reduction product "urobilin" or "stercobilin" formed in the large intestine. It is believed, moreover, that some of the bile pigment is reabsorbed as it passes along the intestine, is carried to the liver in the portal blood, and is again eliminated. That this action occurs, has been

made probable by experiments of Wertheimer[9] on dogs.

The two organic acids, "glycocholic" and "taurocholic", found in the bile are given the name of "bile acids", and they form very important constituents of that secretion. They occur in the form of their respective sodium salts. In human bile, both acids are usually found, but the proportion of taurocholate is variable, and in some cases it may be totally lacking.

Glycocholic acid has the formula $C_{26}H_{43}NO_6$, and taurocholic acid, the formula $C_{26}H_{45}NSO_7$. When boiled with acids or alkalies, these acids take up water and undergo hydrolytic cleavage and the reaction is represented by the following equation: $C_{26}H_{43}NO_6 + H_2O = C_{24}H_{40}O_5 + CH_2(NH_2)COOH$. i.e. the reaction of glycocholic acid and water produce cholic acid plus glycocoll or amino-acetic acid. The reaction of taurocholic acid is: $C_{26}H_{45}NSO_7 + H_2O = C_{24}H_{40}O_5 + C_2H_4NH_2SO_2OH$. i.e. taurocholic acid and water undergoes hydrolytic cleavage as did the glycocholic acid, and form cholic acid plus taurin or amino-ethyl-sulphonic acid.

These reactions are interesting not only in that they throw light on the structure of the acids, but also because similar reactions doubtless take place in the intestine, cholic acid having been detected in the intestinal contents. As shown by the formulas, cholic acid is formed in the decomposition of each acid, and we may regard the bile acids as compounds produced by the synthetic union of cholic acid with glycin in one case and with taurin in the other.

From the standpoint of nutrition, the taurocholate is interesting as giving one of the forms in which the sulphur of protein ma-

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[9] "Archives de physiologie normale et pathologique", 1892, p. 577.

terial is eliminated. Some light has been thrown upon the origin of the taurin by the discovery of Friedmann,[10] claiming that it is formed from cystin. Cystin or its reduction product, cystein, occurs as one of the end-products in the acid hydrolysis of proteins, and it is also possible that it occurs in the tryptic-erepsin hydrolysis in the small intestine, representing the end-product in which the sulphur of the protein molecule is found. It is probable that taurin is formed normally from cystin in the body and that the latter represents one of the split-products of protein.[11] Some of the sulphur of the cystin appears also in the urine in an oxidized form as sulphate. What is of considerable physiological importance is that these acids or their decomposition products are absorbed in part from the intestine and are again secreted by the liver. The value of this reabsorption may be that the bile acids constitute a very efficient stimulus to the bile secreting activity of the cells, as it is one of the best cholagogues, or it may be that it economizes material. It is evident that the bile acids are not to be considered solely as excreta. They have some important function to fulfill. In the first place, they serve as a menstruum for dissolving the cholesterin which is constantly present in the bile and which is an excretion to be removed. Secondly, they facilitate greatly the splitting and the absorption of fats in the intestine. It is an undoubted fact that when bile is shut off from the intestine, the absorption of fats is greatly diminished and it has been shown that the action of the bile in fat absorption is due chiefly to the presence

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[10] Friedmann, "Hofmeister's Bertrage", 3, 1, 1902.

[11] Simon,"Johns Hopkins Hospital Bulletin", 15, 365, 1904.

of bile acids, and so the activating influence of the bile upon the activity of pancreatic lipase has been traced to bile acids.

Besides the bile acids and pigments, there is another constituent termed "cholesterin" or "cholesterol", a non-nitrogenous substance which is found constantly in the bile, although it occurs in variable quantities. Cholesterin is widely distributed throughout the body, being found especially in the medullary substance or white matter of nerve substance. It has been assumed that cholesterin is not formed in the liver, but that it is eliminated by the liver cells from the blood which collects it from the various tissues of the body. It is suggested by other authors, however, that in the dissolution of red corpuscles taking place in the liver, the cholesterin liberated from the stroma of the corpsules forms the source of the cholesterin in the bile. The fact that it is eliminated in the feces indicates that it is an excretum, but the opposite view has been suggested that the cholesterin is in part reabsorbed and used again in the formation of new tissue.[12] We may regard it, however, as far as its occurrence in the bile is concerned, as a waste product of cellular disintegration which is eliminated in the feces. It is also secreted through the skin in the sebaceous and sweat secretions and in the milk.

Lecithin is a compound of glycreophosphoric acid with fatty acid radicals (stearic, oleic or palmitic) and a nitrogeneous base, with the formula, $C_{42}H_{84}NPO_9$. It is generally found as any of the three substances or in combination in all cells, and evidently plays

[12] Gardner, "Proc. Royal Society", B. vols. 81 & 82, 1910.

some part in cell metabolism. It occurs in largest quantities in the white matter in the nervous system. In the liver it occurs to a considerable extent both as lecithin and in a more complex combination with a carbohydrate residue, a compound known as "jecorin". As far as it is found in the bile, it represents a waste product derived from the liver or from the body at large. Little is known of its exact physiological significance.

The special importance of the small proportion of fats and fatty acids in the bile is unknown. The mucilagenous character of the bile is due to the presence of a body formed in the bile ducts and gall-bladder. This substance was formerly known as mucin, but it is now known that in ox bile, at least, it is not a true mucin but a nucleo-albumin.

Composition of Human Bile.

(From Pavlov)

| | Bladder Bile | Fistula Bile. |
|---|---|---|
| Bile Salts | 9.70% | 1.01% |
| Mucin & Pigments | 4.19% | 0.49% |
| Cholesterol | 0.99% | 0.26% |
| Fats | 0.19% | 0.69% |
| Soaps | 1.12% | 0.26% |
| Lecithim | 0.22% | 0.64% |
| Total Solids | 17.03% | 2.98% |
| Inorganic Matter | — | 0.92% |
| Fatty Acids | — | 0.12% |
| Water | 82.97% | 97.02% |

### c. General Physiological importance of Bile.

Bile is probably important both as a medium of excretion and as a secretion taking part in the digestion of food. Little is known of it from the former point of view. It is difficult to ascertain just how far certain of its constituents are to be regarded as excretory products; they may appear in the feces more or less modified but on the other hand, they may be reabsorbed in part from the intestines. It can be shown experimentally that a number of dyes when introduced into the blood are eliminated or excreted by way of the bile as well as through the urine, indicating that the liver may play the part of an excretory organ.

The most important function that may be attributed to the bile as a digestive secretion, is the part which it takes in the digestion and absorption of fats. It accelerates the action of the lipase of the pancreatic juice in splitting the fats to fatty acids any glycerin and it acts as an aid in the absorption of the products of this hydrolysis. It has been shown by experimentation that when a permanent biliary fistula is made, and the bile is prevented from reaching the intestinal canal, a large portion of the fat of the food is found in the feces having escaped absorption. Hence, it is shown that the bile acids serve as a solvent for the fats and fatty acids.

It was originally believed that bile was also of great importance in inhibiting the processes of putrefaction within the intestine. It was considered as an efficient antisceptic, and that this property came into use in preventing excessive putrefaction. It

has been shown by bacteriological experiments, however, that bile possesses very feeble antisceptic properties, as is indicated by the fact that it putrefies readily. In cases of biliary fistula, it seems generally true that the feces have a fetid odor when meat and fat are introduced into the food. The increased putrefaction, however, in these cases may be due to an indirect result of the withdrawal of bile. It has been suggested that the deficient absorption of fat following upon the removal of the bile, results in the protein and the carbohydrate material of the food becoming coated with a layer of fat, retarding the penetrating action of the digestive enzyme and affording a greater opportunity for the occurrence of bacterial action.

Hence, we may conclude that while there is not sufficient reason at present for believing that the bile exerts a direct antisceptic action upon the contents of the intestine, its presence, nevertheless, limits to some degree the extent of putrefaction.

## Formation of Glycogen

One of the most important functions of the liver is the formation of glycogen. This substance was discovered by Claude Bernard in 1857, and is one of the brilliant discoveries made by him.

Glycogen has the formula $C_6H_{10}O_5$, the formula given also to animal starch, hence, glycogen is often spoken of as animal starch. It is readily soluble in water, and the solutions have a character-

istic opalescent appearance. Glycogen, like starch, is acted upon by ptyalin and other diastatic enzymes and the end-products are the same, viz. maltose and dextrin or dextrose depending upon the enzyme used.

If the liver of a dog were removed twelve or fourteen hours after a hearty meal, hardened in alcohol and sectioned, the cells would be found to contain clumps of clear material which give the iodin reaction for glycogen. The red reaction with iodin shows the presence of the glycogen in the cells even when distinct aggregations of it cannot be made out. This simple method demonstrates the fact that the amount of glycogen in the liver increases after meals and decreases during fasting hours, and if the fast is sufficiently prolonged, it may disappear entirely.

The amount of glycogen present in the liver is variable, being influenced by such conditions as muscular exercise, body temperature, drugs and amount of food. From quantitative determinations in various animals, it may be said that the average amount lies between 1.5 and 4 per cent. of the weight of the liver. This amount, however, may be greatly increased by feeding upon a diet made up largely of carbohydrates. It is generally taken for granted that glycogen exists as such in the liver cells deposited as such in the cytoplasm. However, reasons have been brought forward to show that this is not strictly true, and that the glycogen is held in some sort of weak chemical combination.

For practical purposes, glycogen may be spoken of as lying free in the liver cells, as we speak of haemaglobin existing as

such in the red corpuscles, though it is, no doubt, held in some sort of combination.

To understand clearly the views held in regard to the origin of glycogen in the liver, it is necessary to describe the effect of the different food-stuffs, as protein, carbohydrates and fats, upon its formation. The amount of glycogen in the liver is quickly affected by the amount of the carbohydrates in the food. If the carbohydrates are given in excessive quantities, the supply of glycogen may be increased beyond the average amount. Experimentation upon the different sugars has shown that dextrose, levulose, saccharose or cane-sugar, and maltose are direct glycogen formers, i.e. glycogen is formed directly from them or from the products into which they are converted during digestion. The greatest portion of our carbohydrate food reaches the liver as dextrose, or as dextrose and levulose, and these forms of sugar may be converted into glycogen in the liver cells by a simple process of dehydration represented by the formula: $C_6H_{12}O_6 - H_2O \rightarrow C_6H_{10}O_5$. Since cane-sugar is inverted in the intestine before absorption, it must also be a true glycogen former, a fact which has been amply substantiated by direct experiment.

[13] Lusk has shown that if cane-sugar is injected under the skin, its effect in increasing the amount of glycogen in the liver is very feeble since under these conditions it is probably absorbed into the blood, without undergoing inversion. Experiments with subcutaneous injections of lactose give like results and it is generally believed that the liver cells cannot convert them to glycogen; hence, may be

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[13] Voit, "Zeitchrift f. biologie", 28, 285, 1891.

seen the value of the hydrolysis of the sugars in the alimentary canal before absorption. We may assume then that dextrose, levulose, and galactose are the true glycogen formers that occur in the blood, and that the disaccharids and polysaccharids are true glycogen formers to the extent that they are converted into dextrose, levulose and galactose.

Bernard, in his first studies upon glycogen, asserted that it might be formed from protein material. Since his time there have been many discussions upon this point. The general view is that protein must be considered as a true glycogen former in the sense that some of the material of the protein molecule is converted directly to glycogen. The protein in digestion undergoes a splitting process and it is assumed that the nitrogenous split products are acted upon in the liver, the nitrogen being first converted into an ammonia compound and then to urea, while the non-nitrogenous residue is converted to sugar by a synthetic process.

# PART 4.

## THE PANCREAS

### Gross Anatomy

The pancreas is an elongated, glandular mass lying transversely on the posterior abdominal wall, with its right end resting in the concavity of the duodenum and its left end touching the spleen. The head is placed opposite the second and upper part of the third lumbar vertebra while the body runs to the left about on the line with the first lumbar vertebra. Its total length when fixed in place is about 5 or 6 inches; its weight is about 3 ounces.

The body is of prismatic form, largest where it lodges in front of the left kidney and usually somewhat tapering towards the tail. Beginning at the termination of the neck, it runs backwards and to the left across the front of the left kidney beyond which its extremity or tail comes in contact with the spleen.

Invariably two ducts are found in the interior of the pancreas - the pancreatic duct proper and the accessory pancreatic duct. The pancreatic duct begins near the tip of the tail by the union of the small ducts from the lobes forming that part of the organ. From this it pursues a zigzag course through the axis of the gland at first running transversely to the right until the neck is reached, then bending down towards the head. Here it approaches the second portion of the duodenum and meeting the bile duct, the two pierce the inner wall of the gut obliquely and open, by a common orifice

on the bile papilla beyond the pylorus.

The accessory pancreatic duct is a small variably developed duct which opens into the duodenum about ¾ inches above and somewhat in front of the pancreatic duct. From the duodenum it runs to the left and downwards and divides into two or more branches, one of which forms the union with the pancreatic duct, the others pass down and recieve the ducts from the lower part of the head. It is supposed that the current flows from this into the main duct and not into the duodenum except in early life.

Though in the adult the pancreas is a single gland, it arises in the embryo as two entirely distinct entodermal outgrowths known respectively as the dorsal and ventral pancreas. The dorsal pancreas grows out of the dorsal wall of the intestinal tube, a little below the level of the common bile duct in most mammals, but a little above it in man. The ventral pancreas grows down from the common bile duct at its junction with the intestinal tube; it may be more or less bi-lobed. It usually grows to the right of the intestine and there meets the dorsal pancreas, which approaches it in close relation with the portal vein.

The dorsal pancreas is much larger than the ventral and it grows across the body toward the left until it reaches the spleen. Thus, it gives rise to the body and tail of the pancreas of the adult and it also forms the ventral part of the head of the gland which fills the concavity in the duodenal loop.

In Fig. 7 is shown a diagram of the pancreas from a 15 m.m. human embryo; in Fig. 8 is shown a dissection of the duodenum and pancreas of an adult.

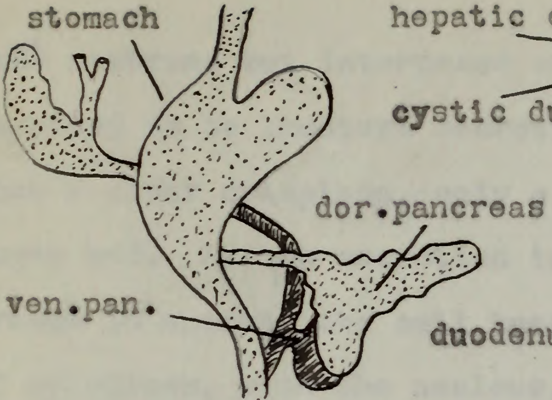
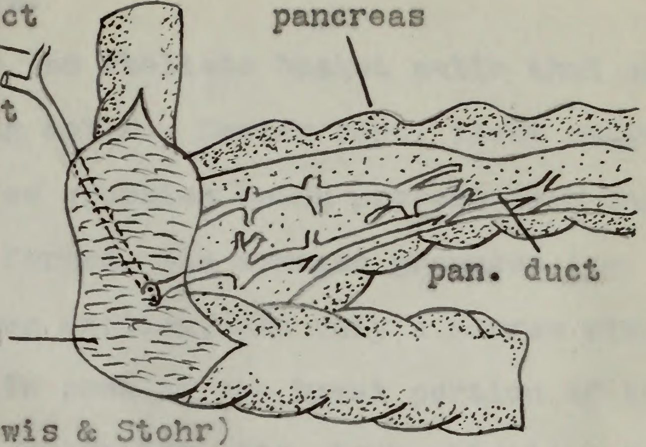


Fig. 7.



(After Lewis & Stohr)

Fig. 8.

## Histological Structure

In the adult no histological distinction has ever been found between the two pancreases; although alike in structure and close together, there is no general anastomosis between them. They rarely remain entirely separate. Upon injecting the ducts, only one connection is found between the dorsal and ventral pancreas, but two connections have been observed in an abnormal case. Anastomoses between the smaller ducts and tubules in the separate glands have been found in human adults.

The pancreas is the other serous gland and is compound alveolar in structure. It is also called the abdominal salivary gland. Its general structure is somewhat similar to that of the parotid, but its lobes contain the secreting units, or acini that are larger than those of the parotid. These acini are distinct, sharply outlined and stain darkly. The cells lining an acinus are of the pyramidal type and the amount of lumen showing will depend upon the stage of secretory activity. The cells rest upon a base-

ment membrane but interposed are the stellate basket cells that are supposed to be immature secreting cells. During rest, these cells show a clear cytoplasm, only a few granules being present near the lumen end. As the secretion is formed, the zymogen granules increase in amount, the cell becomes swollen, and only a narrow rim of cytoplasm, with the nucleus, is seen at the basal portion of the cell. With the discharge of the secretion, the clear cytoplasm increases and spreads through the cell, which is much smaller in size. The nucleus plays an important part in the secretion. The paranucleus is seen in the active cells.

In the basal portions of the cells mitochondrial filaments are readily demonstrated. These are said to give rise to the zymogen granules but some believe that they are concerned only with the metabolic activities of the cell.

Within many of the acini are seen lightly staining flattened elements that are called the centro-acinar cells. These are characteristic of the pancreas and represent the squamous cells of the intercalated tubules invaginated into the acinus. They are separated from the secreting cells by intercellular secretory capillaries.

In addition to the acini, numerous groups of lightly staining cells are scattered throughout tubules; these are the pancreatic islands or "Areas of Langerhans". They are oval or circular in outline each surrounded by a delicate capsule that sends in tuabeculae that seem to arrange the cells into irregular groups or cords. The number of cells in an island varies from several to many so that these islands may be microscopic or macroscopic. The cytoplasm of these

cells stain slightly and contain some fine eosinophilic granules that are supposed to be of two kinds and, therefore, form two kinds of secretions. The blood vessels are of the sinusoidal type and are in close relation to the cells, forming glomerule-like masses in injected secretions. They possess no outlet for the secretion that they form and this is said to pass directly to the blood capillaries.

Recently Banting and others succeeded in making an extract of the islands alone which was called "insulin". Injections of this substance have been used with great success in patients suffering from diabetus mellitus. The sugar metabolism in these patients is controlled if injections are taken regularly.

The islands are most numerous in the splenic end of the pancreas and very considerably in number. They may be increased in size and number by means of secretion, and in long hunger they are also increased, It is claimed that there is a connection or lumen between the islands and the acini in reptiles and fishes. In man, this connection apparently does not exist, as ligation of the pancreatic duct does not affect the islands nor does it interfere with carbohydrate metabolism. In some cases, if the islands are diseased, or if the pancreas of animal be removed, diabetus mellitus follows. The areas, post-mortem, show degenerative changes. The excretory duct or "the duct of Wirsung" is lined by simple columnar cells.

## Composition of the Secretion

The secretion of the pancreas is an alkaline liquid which in some animals is thin and limpid while in others is thick and glairy. The secretion in man is of the former description, as clear as water and with a specific gravity of 1.0075. The secretion may be collected by opening the abdomen and inserting a cannula into the duct or a permanent fistula is made in the manner according to Pavlov. This method consists in cutting out a small portion of the duodenum where the pancreatic duct opens, and then suturing this piece, the mucous membrane outward, into the abdominal wall. The secretion then pours to the exterior and may be collected.

According to the observations made by Glaessner,[14] it appears that the secretion in man is quite abundant, amounting to 500 to 800 c.c. per day. The secretion possesses a strong alkaline reaction due to the presence of the sodium carbonate. It also contains a small amount of coagulable material which is protein and a number of organic substances in traces.

It is important to note that the alkalinity of the juice corresponds almost exactly to the acidity of the gastric juice.

In one experiment,[15] 70 c.c. of pancreatic juice obtained by injection of secretin, required 78 c.c. of 4% hydrochloric acid for their complete neutralization. Each portion of the chyme ejected from the stomach into the duodenum will continue to excite the production of secretin in the epithelial cells until, under the influence of the absorbed secretin, the pancreas has poured out an equal quan-

[14] Glaessner, "Zeitschrift f. physiologie chemie", 40, 465, 1903.

[15] Starling, "Recent Advances in the Physiology of Digestion", 1906.

tity of pancreatic juice and the duodenal contents are thus neutralized. The pylorus will then open and allow a further portion of acid chyme to pass into the duodenum, to excite in the same way the secretion of a further equivalent portion of pancreatic juice. Since under normal conditions a secretion of the bile occurs at the same time as the pancreatic secretion, and since bile has a power of neutralizing the acid of the chyme, it is probable that under normal conditions the secretion of the pancreatic juice will be rather smaller in amount than the chyme passing through the pylorus. The neutralizing effects of these two juices is aided, moreover, by the secretion of an alkaline juice by the intestinal glands. The final result is the production of a neutral fluid in the duodenum, and it is in this neutral fluid that the processes of intestinal digestion will take place.

Pancreatic juice contains ferments which act as strong hydrolytic agents on starchs and fats. Starch is rapidly converted by the juice into dextrin and maltose, and the maltose is more slowly transformed into glucose. The neutral fats are converted into glycerin and fatty acids. Juice obtained from a temporary fistula has a very slight action on proteids. Fresh fibrin and caseinogen are slowly digested. Therefore, the juice may be said to contain a weak proteolytic ferment, resembling that which can be extracted from almost any tissue of the body. A similar ferment can be obtained from extracts of the intestinal mucous membrane, and has been named "erepsin". Its chief function seems to be the further digestion of albumoses and peptones, and their conversion into amino-acids. All the greater physiologists, among whom Kuhne, Heidenhain and Langley may be given

special mention, found that the watery extract contained not only a lipase, a lypotlytic enzyme, and amylase, but also a substance which rapidly underwent conversion into an active proteolytic ferment.

## Normal Mechanism of the Secretion.

The pancreas resembles the salivary glands in that it is composed of a mass of compound tubular glands. It pours its secretion together with the common bile duct into the duodenum. It is easy, then, to establish a temporary fistula by isolating the duct before it joins the intestine, and thus determine the normal relation of the secretion of the pancreatic juice to the process of digestion.

Following is a table showing the secretion of the pancreatic juice resulting from a meal of 600 c.c. of milk compared with the secretion of gastric juice evoked by the ingestion of 100 grams of meat.

Gastric secretion after a meal of 100 grams of meat.

(two experiments)

| Hour after feeding. | Quantity of juice in c.c. | |
|---|---|---|
| 1st . . . . . . . . . . . . | 11.2 | 12.6 |
| 2nd . . . . . . . . . . . . | 8.2 | 8.0 |
| 3rd . . . . . . . . . . . . | 4.0 | 2.2 |
| 4th . . . . . . . . . . . . | 1.9 | 1.1 |
| 5th . . . . . . . . . . . . | 0.1 | a drop |
| Total | 25.4 | 23.9 |

(After Pavlov)

Pancreatic secretion after meal of 600 c.c. of milk.
Two Experiments

| Hour after feeding | Quantity of juice in c.c. | |
|---|---|---|
| 1st | 8.75 | 8.25 |
| 2nd | 7.5 | 6.0 |
| 3rd | 22.5 | 23.0 |
| 4th | 9.0 | 6.25 |
| 5th | 2.0 | 1.5 |
| Total | 49.75 | 45.0 |

It can be noticed that, whereas the greatest quantity of gastric juice is poured out in the first hour after the meal, the maximum flow of pancreatic juice occurs in the third hour at the time when the largest amount of chyme is passing from the stomach into the duodenum. Hence, there must be some causal relationship between the passage of the food through the pylorus and the secretion of the pancreatic juice. It is only of late years that the nature of the connection between these two events has been brought to light. The flow occurring upon the passage of acid chyme into the duodenum was ascribed to the intermediation of a reflex arc. Difficulty, however, was experienced in the search for the channels of the reflex. Pavlov was able to obtain a flow of the juice upon the stimulation of the vagus and splanchnic nerves, and he, therefore, regarded pancreatic secretion as determined, either reflexly or psychically, through the cortex by impulses leaving the central nervous system and traveling to the gland along one of these two sets of nerves.

Wertheimer and Popielski, a pupil of Pavlov, both showed that the secretion of the juice, evoked by the introduction of acid into the small intestine was unaffected by division of both vagus and splanchnic nerves, by excision of the spinal cord, or by the exterpation of the abdominal sympathetic. Therefore, they regard the secretion as being due to a local reflex, starting with the mucous membrane of the gut and thence traveling to the collections of ganglionic cells which are found in large numbers in the pancreas. These collections acted as reflex centers which transmitted secretory impulses directly to the pancreas.

Bayliss and Starling instituted a research with a view to determining the conditions and paths of this local secretory reflex. In one experiment, a loop of the upper part of the jejunum was ligatured at two ends and then 25 c.c. of 4 per cent. hydrochloric acid was introduced. A flow of pancreatic juice was obtained. Then all possible nervous connections between the loop and the pancreas were destroyed. Both splanchnic and vagi nerves were cut, the abdominal sympathetic ganglia round the big vessels extirpated, and all the nerve filaments traveling along the vessels to the ligatured loop were dissected away. At the same time the mesentery was divided so that the loop of the intestine was connected to the rest of the body only by its blood vessels. Acid was then introduced for the second time into the lumen of the gut. Though all nervous connections between gut and pancreas had been destroyed, the reaction was the same as in a normal animal, and an abundant flow of juice was obtained.

The experiment proved at once that there was no question of a

nervous reflex, either central or peripheral, but that the connection between the mucous membrane and pancreas must be chemical and be effected through the blood. From Wertheimer's researches, we know that the direct introduction of acid into the blood produced no flow of pancreatic juice. The question, then, is what was the difference between the introduction of acid into the gut, which did produce a flow, and its introduction into the blood which did not produce a flow? The sole difference was taken to lie in the layer of epithelial cells, which intervene between the lumen of the gut and the capillary blood vessels in the interstitial villi. In these cells some substance must be produced under the action of acids, which on absorption into the blood, acts as the chemical messenger to the pancreatic cells. The hypothesis was tested. The loop of the intestine was cut out, the cells lining the mucous membrane scraped off and mixed with dilute hydrochloric acid. The extract was filtered, and the injection of the filtrate into the animal's veins was found to produce a flow of juice even greater in extent than that excited by the introduction of acid into the lumen of the gut. This substance, formed in the cells under the influence of the acid was called "secretin". Since it is not destroyed by boiling, it is not a ferment. It is diffusible and soluble in alcohol or alcohol and ether.

It was concluded, then, that the epithelial cells lining the gut contain a body - "prosecretin", which is insoluble in water, alcohol or salt solution, but which under the influence of agents such as acids, undergoes hydrolysis with the splitting off of a new body - secretin. That this mechanism is normally involved in the produc-

tion of pancreatic secretion and is responsible for the flow obtained on the introduction of acid into the intestine, is shown by the fact that its distribution in the gut exactly corresponds with the Wertheimer's results. Thus, whereas an extract of the mucous membrane of the duodenum yields a very strong solution of secretin, a similar acid extract of the lower two feet of ileum yields a solution which has no influence on the pancreas.

## Digestive Action of Pancreatic Juice.

Fresh juice has a strong amiolytic action on starch, and a slight fat-splitting action which is largely increased by the presence of bile. If fresh fibrin is allowed to remain in contact with the juice at a temperature of 38 C., it is unaltered at the end of one or two hours, but at the end of 24 hours it is completely dissolved. This action on fibrin has been ascribed by Delezenne[16] to the presence of "enterokinase" in the fibrin derived from the disintegration of leucocytes.

Pancreatic juice also hydrolyses caseinogen, though slowly, and the proteolytic ferment in the juice apparently attacks the proteids of the juice itself. Hence, if the juice is kept for some time, and then treated with trichloracetic acid, the filtrate will give a slight but distinct biuret reaction. Pancreatic juice is without effect on coagulated proteid or on solid gelatin at the temperature of the room. Coagulated egg-albumen may be kept in contact with the juice for a

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[16] C.R.Soc. de Biologie, 1902, p. 591.

week without undergoing solution.

Fresh juice may be kept for weeks without any apparent alteration in their feeble proteolytic power. It is evident, then, that this power is not due to a partial spontaneous conversion of the trypsinogen into trypsin. This latter ferment makes no qualitative difference between coagulated and dissolved or uncoagulated proteid. It may be so largely diluted that its action on fibrin is reduced to the feeble degree which is characteristic of fresh pancreatic juice. In this dilution it still digests coagulated egg white and gelatin slowly whereas fresh pancreatic juice which will digest fibrin in 24 hours is without effect on coagulated egg albumen even after the lapse of a week.

It is believed by Bayliss and Starling[17] that the outgrowth of the intestinal epithelium which gives origin to the pancreas retains one primitive function of the intestinal epithelium, viz. the power of secreting a very feeble proteolytic ferment, and would describe the pancreatic juice as containing a ferment similar to that described by Cohnheim and named by him "erepsin". The case is different, however, when an extract of the intestinal mucous membrane is added to the fresh juice. Within a short while the juice becomes most powerful as a proteolytic agent, one which, at body temperature, will digest fibrin within 10 minutes,and tubes of coagulated egg white within a few hours.

The activated trypsinogean brings about a hydrolytic cleavage of the protein molecule in a manner similar to that described for pepsin. It differs in action, however, from pepsin in many ways. It attacks the protein in neutral as well as in the slightly acid or

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[17] Bayliss and Starling, "Journal of Physiology", p. 66, 1904.

strongly alkaline solutions. Its effect upon the protein is more rapid and powerful than that of pepsin and the protein molecule is broken up more completely. The pepsin and trypsin really act in cooperation with one another; the change begun by the pepsin is completed by the trypsin.

The actual products formed by the action of trypsin depend on the length of time the trypsin is allowed to act, and the conditions, favorable or unfavorable, under which it acts. The end-products usually formed are, trypsin, leucin, aspartic acid, glutaminic acid, tryptophan, lysin, arginin, histidin. If the trypsin is allowed to exert complete action on the protein, the end-products are closely similar to those obtained by boiling protein with acids. The product would consist chiefly of amino-acids, that is, organic acids containing one or more amino groups ($NH_2$) in direct union with carbon. Some of the amino bodies are monoaminic acids, that is, they contain one $NH_2$ group, such as leucin, tyrpsin, glycin and include substances belonging to the series of fatty acids.

The diastatic enzyme is found in the secretion of the pancreas or it may be extracted from the gland. Its action upon starchy foods is similar to that of ptyalin. It brings about a hydrolysis of the starch with the production finally of maltose and acroödextrin. Before absorption, these substances are further acted upon by the maltase of the intestinal secretion and converted to dextrose. The starchy food that escapes digestion in the mouth and stomach becomes mixed with this enzyme in the duodenum, and from that time until it reaches the end of the large intestine the conditions are favorable for its conversion into maltose and dextrin. Most of this digestion is, no doubt

completed before the contents of the intestinal canal reach the ileocecal valve.

The pancreatic secretion contains an active enzyme, lipase, which is capable of hydrolyzing or saponifying the neutral fats. These neutral fats are chemically esters of the trihydric alcohol glycerin. When hydrolyzed they break up into glycerin and the constituent fatty acid. The action of lipase, then, may be represented by the following reaction in the case of palmitin: $C_3H_5(C_{15}H_{31}COO)_3 + 3H_2O \rightleftharpoons C_3H_5(OH)_3 + 3(C_{15}H_{31}COOH)$. When lipase is added to neutral oils, its splitting action is easily recognized by the development of an acid reaction due to the formation of the fatty acid. For example, if a piece of fresh pancreas is added to butter, and the mixture kept at body temperature, the hydrolysis of the fats is made evident quite soon by the rancid odor due to the production of butyric acid. When pancreatic juice is mixed with oils or liquid fats, there is first, a splitting of the fat already referred to, and secondly, an emulsification of the fat. An oil is emulsified when it is broken up into minute globules that do not coalesce. Artificial emulsions may be made by vigorous and prolonged shaking of the oil in a viscous solution of soap. It is now known that the emulsification of oils and fats is due to the formation of soaps.[18] The lipase splits some of the fats and the fatty acid liberated combines with the alkaline salts present to form soaps. The emulsification under these conditions is very fine and very permanent.

It was formerly believed that the formation of this emulsion was the main function of the pancreatic juice so far as fats were concerned. It was thought that in the form of fine droplets the fat may be taken up directly by the epithelial cells of the villi, and this view

[18] Ratchford, "Journal of Physiology", 12, 27, 1891.

was supported by the histological fact that during the digestion of fats the epithelial cells may be shown to contain fine oil drops in their interior. The tendency of recent work, however, has been to show that the fats are completely split into fatty acids and glycerin before absorption, and that the emulsification may be regarded, from a physiological standpoint, as a mechanical preparation for the action of lipase rather than as a direct preparation for the action of absorption. The two products of the action of lipase, the glycerin and fatty acid, are absorbed by the epithelium and again combined to form neutral fat.

According to Loevenhart,[19] it seems quite possible that the same enzyme may cause both the splitting of the fat and the synthesis of the split-products, not only in the intestines before absorption, but in the various tissues during the metabolism or storage of fat. Lipase is found in the blood and in many tissues, and during its nutritive history in the body, the fat may be split and synthesized a number of times. The splitting process does not involve much work and very little heat is liberated, and a correspondingly small amount of energy is needed for the synthesis.

The action of lipase is aided materially by the presence of bile. This latter secretion contains no lipase, but mixtures of bile and pancreatic juice split the neutral fats more readily than the pancreatic juice alone. This is now explained on the hypothesis that the bile acids or the bile acids and the lecethin activate a portion of the lipase which is in a state of a proferment.

[19] Loevenhart, "American Journal of Physiology", 6, 331, 1902.

## PART 5.

## THE DUODENAL GLANDS

The walls of the small intestine are composed of the same four coats described as composing the walls of the stomach, the mucosa, submucosa, muscularis and serosa.

The submucosa consists, as in the stomach, of loosely arranged connective tissue and contains the larger blood vessels. It is free from glands except in the duodenum where it contains the "glands of Brunner". These are branched tubular glands lined with a granular columnar epithelium similar to that of the pyloric glands. The ducts are also lined with a simple columnar epithelium. They pass through the muscularis mucosae and empty either into a "crypt of Lieberkuhn" or on the surface between the villi. Brunner's glands frequently occur in the pylorus and it is not uncommon for the pyloric glands to extend downward somewhat into the duodenum.

To the naked eye examination they are small, rounded or flattened masses of a reddish gray color varying in size from one fiftieth to one twelfth of an inch in diameter (.5 to 2.0 mm.) They form an almost continuous layer as far as the opening of the bile duct; beyond this they diminish progressively and completely disappear near the duodenal-jejunal flexure.

The presence of the glands in the duodenum was discovered in 1679 by Wepfer who observed that, when macerated in water, the glands liberated an abundant amount of mucus. The glands were described more fully eight years later by Brunner who regarded them as a sort

of secondary pancreas. Claude Bernard and Middeldorph, however, showed the incorrectness of this view and pointed out how the secretion of the glands of Brunner differed from that of the pancreas.

Budge and Krolow in 1870 found that the extract of the glands of Brunner would transform starch into sugar, would dissolve fibrin in acid solution, but would not act upon coagulated egg albumen nor upon fats.

In 1902, Glassner extended to the study of the glands of Brunner the methods which he had employed with success to separate the various ferments of the gastric mucous membrane. The extracts which he obtained, after excluding the glands of Lieberkuhn from the extracted material and destroying the adherent pepsin and trypsin, were not active to starch, cane sugar and fats, but on the other hand, digested fibrin, serum albumen, and coagulated egg albumen in solutions containing .2 to .3 per cent. hydrochloric acid. The specific ferment upon which depended this proteolytic action, he identified with the pseudopepsin which he had formerly extracted from the pyloric mucous membrane. It differed from pepsin in that it was not destroyed, nor its activity removed by weak solutions of sodium carbonate. Also, its action quickly led to the formation of tryptophan. It was distinguished from trypsin by its activity in acid solutions.

Whether this is a tissue enzyme concerned in the various metabolic processes of the cell itself or a secreted product of the cell designed to assist in the intestine in the transformation of the proteids of the food is not definitely known.

Anatomically, the main points of interest are the form and distribution of the glands, the question as to whether they are serous

or mucous glands, the changes they exhibit in different stages of physiological activity and their relationship to the pyloric glands.

The question concerning the form of the glands has been adequately treated by Schwalbe (1872) whose conclusions were that the glands of Brunner are composed of ramifying tubules into which acini open.

There has not been the same unanimity of opinion concerning the mucous or serous nature of the glands. This has been due to, first of all, the close resemblance of the glands of Brunner to the pyloric glands of the stomach which Heidenhain (1870 - 1878) had shown on physiological grounds to be pepsin-forming serous glands. A second cause contributing to the confusion of results is the lack of precision in the morphological criteria for distinguishing between mucous and serous cells.

As there has been no specific data obtained in regard to the nature of the cells, we must, therefore, compare them as regards structure, staining and microchemical reactions, and the changes they exhibit in different phases of functional activity, not only with the adjacent gastric and intestinal glands, but also with the many glands from other sources that have been the subject of exact investigation.

Most writers agree on the point that there is a great similarity between the glands of Brunner and the pyloric glands of the stomach, although researches of Castellant (1898), Kuczynski (1890) and others do not confirm the conclusions of Benthowski (1876) and Schieferdecker (1884) that the two types of glands are identical.

The question of relationship of the glands of Brunner to the pyloric glands is interesting from the standpoint of the phylogenesis of the former glands. The fact that they have been found with-

out exception in all mammals belonging to the classes in which they have been sought, shows that they must have appeared very early in the history of Mammalia. The fact that the pyloric glands and the glands of Brunner have been subject through this long phylogenetic history to diversified conditions would alone be sufficient to explain slight differences in the nature of their cells, even though the two sets of glands came from a common origin.

Furthermore, in many groups of animals, owing to a change of food habits, the stomach has undergone important adaptive modifications, resulting in the suppression of extensive areas of gastric glands and the replacement of cylindrical epithelium by stratified squamous epithelium, and the modification in type of the remaining glands. It is reasonable to expect that under these conditions, the pyloric glands would be modified and the differences between them and the glands of Brunner more pronounced. It would be unfair to assume that, because the pyloric gland cells differ from those of the glands of Brunner in an animal with such a specialized stomach, they are primitively different. In other words, in discussing the question of the difference or similarity of the two sets of glands, both the long phylogenetic history of the glands and the relative visceral specialization of the animal under investigation must be given due consideration.

# PART 6.

## CONCLUSIONS

Though one should make a sincere attempt to treat the physiology of the digestive glands as thoroughly as possible with the present available data, the subject would be, in reality, far from exhausted. A great deal remains to be achieved before there is a complete conquest of the territory. What has been already gained is very valuable as a guide to future research. There are very many more inquiries which are constantly arising, all of which mean progress in future investigation, since they testify to the existence of a wide field of research which has been studied more or less from a general point of view.

We have seen the great complexity and at the same time the marked constancy and accuracy of the work of the digestive glands. It now becomes necessary to seek an explanation for every step of this complicated process. The different food constituents must be studied individually and more thoroughly in order to determine more fully their particular significance. It is from the effects of the elementary constituents that each point of the curve of secretion after a complex meal must be explained.

As has been suggested by Pavlov, to solve this problem the individual constituents of the foods must be successively combined with each other, and the food synthetically built up step by step while at the same time the properties of the juice must be sub-

mitted at every phase to an exact analysis. In the case of complex foods, better conclusions can be drawn from the properties of the juice as to what has been the effective excitant. The systematic investigation of the constituents of the food in this manner will undoubtedly lead to the discovery of many unexpected relationships between the foodstuffs and the digestive glands.

A complete and accurate answer as to why and in what way gland activity varies can be obtained only when an exact investigation of the contents of the alimentary tract is joined closely with observations upon secretory activity; for example, when for every period of digestion, and for every secretion of the digestive canal, we know exactly where a particular constituent of the food could be found and exactly what nature of alterations it may be undergoing.

Questions must also be considered that deal with the seat of action of the elementary food constituents, their mode of working, and the combined results of their local excitants. This would naturally involve the chain of phenomena in the central nervous system given an impulse by the peripheral excitations from the digestive tract as well as the impulses from other organs. The two questions last mentioned are very closely linked.

After a thorough study of the alimentary canal and its accessory organs of secretion, we are able to see delineated an intricate mechanism which, like other things of nature, is adapted with the utmost delicacy and precision to the task it has to perform. An advantage to the digestive process is gotten from the instinctive craving for food; in addition to the impulse to seek and par-

take of food, the instinct is at the same time connected with the first and strongest secretory impulse to the gastric and salivary glands. Through the medium of this the stimulus is transmitted further to other digestive organs. The fluids differing in reaction transform a considerable part of the food into a soluble half-fluid condition and so allow the chemical constituents of the mixture to take effect. As a result of this, the initial rate of gland activity is modified in order to harmonize with the altered conditions of the food which by this time are such that they are capable of stimulating the end-organs of the neuro-secretory apparatus. A certain equilibrium is maintained both in regard to the quantity and the strength of the digestive medium as a whole. The transformation of one constituent is favored, that of another restrained. The secretory work which started with the ingestion of food is passed on from stage to stage along the alimentary tract due to a suitable and harmonious linking of the several consecutive processes.

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